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ANNALS OF INTERNAL MEDICINE

PUBLISHED MONTHLY BY

The American College of Physicians

VOL. 35 (O.S., Vol. XL) JULY, 1951 NUMBER 1

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Entered as Second Class Matter August 21, 1933, at the Post Office at Lancaster, Pa., under the Act of March 3, 1879. Acceptance for mailing at a special rate of postage provided for in the Act of February 28, 1925, embodied in paragraph (d-2), section 34.40, P. L. & R. of 1948, authorized October 7, 1936.

ANNALS OF
INTERNAL MEDICINE

VOLUME 35 JULY, 1951 NUMBER 1

THE DESTINY OF THE AMERICAN COLLEGE OF PHYSICIANS *

By WILLIAM S. MIDDLETON, F.A.C.P., *Madison, Wisconsin*

"Your old men shall dream dreams; your young men shall see visions." Joel II, 28.

By Roman law the collegium was a corporation established for the control and administration of medicine. In the Middle Ages the College of Physicians of Rome, composed of highly representative physicians, assumed complete supervision of all practitioners of the healing arts and allied activities in that city. Florence was the scene of a college's most effective operation in Italy. From this city the movement infiltrated the rest of Europe and Great Britain with certain deviations in form and function determined by local or national circumstances. In Central Europe the guilds prevailed and the professional college never won sustained support. The French colleges were multiplied; but the dominance of the Faculté de Médecine effectively prevented the continued growth of a college of physicians in Paris.

As our lineal prototype, the College of Physicians of London naturally arrests the attention. Never was it more truly said, "Every great institution is the lengthened shadow of a single man." Thomas Linacre (1460–1524) attended the cathedral school of Canterbury under William Celling, who later (1472) became the prior of Canterbury. When Henry VIII named Celling his envoy to the papal court, the latter in turn invited Linacre to accompany him to Italy. Linacre left Oxford and went with his old master as far as Bologna. He later moved to Florence to improve his educational opportunities. His medical degree was taken with honors at Padua. Returning to Oxford he surrounded himself with a coterie of learned and scholarly associates, illuminated by the brilliant light of the Italian Renaissance. Linacre found favor in the royal household and was called to court to tutor Prince Arthur. Upon the accession of Henry VIII to the throne (April 22, 1509) he was made king's physician. His private practice was

* Presidential Address, Thirty-Second Annual Session, American College of Physicians, St. Louis, Mo., April 9, 1951.

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likewise highly successful. Yet his vision was undimmed. He retained a clear picture of the fine contribution of the Florentine College to the standards of medical practice, and aspired to emulate this worthy example in London. Through his unselfish influence, Henry VIII granted the charter of the College of Physicians of London in 1518. Nor was Linacre satisfied with this regal formality. He gave the College its first meeting place, served as its first president and established its library through the gift of his books. The debt of medicine to this scholarly physician, humanist and devout churchman can never be discharged.

Traditionally the College of Physicians of London ("Royal" designation added later) incorporated three functions; namely, academic, administrative and medico-political. In the absence of well organized departments of medicine in the universities, the College encountered no early opposition to its academic programs of teaching, examining and awarding diplomas and degrees. However, the preëmption of the authority to contest the adequacy of training in the universities eventually led to sharp conflict and acrimonious civil suits between the College and the medical faculties. From the administrative angle, the College was admittedly in a strategic position to regulate the practice of medicine and medical ethics. Through the years this function has brought great credit to the corporation. The medico-political activities have fluctuated widely from time to time. In the main they have been confined to advice to the government on matters pertaining to health, but on occasions the College has embarked upon discussions of more involved policy.

The chronicle of the Royal College of Physicians of London is literally a record of the ideals, ambitions and achievements of Anglo-Saxon medicine. Its traditions afford a worthy charter for similarly motivated bodies the world over. Yet at one period, its provincialism, which excluded all save residents within seven miles of the center of London and graduates of medical schools other than Cambridge and Oxford, almost sealed the doom of the College. Indeed, Lord Justice Mansfield saw fit from the bench to caution against so restricted a policy, "which might exclude even a Boerhaave." Reason prevailed. The universities took their proper place in medical education. With certain liberalization, the qualifications were broadened and the standards of Fellowship in the College maintained. Artificial strictures were removed to admit physicians of superior attainments and responsibilities from all parts of Great Britain and the British Empire.

A proper chronological account of the Royal College of Physicians of London, fascinating though it is, falls beyond the present purview. However, certain details of organization and operation may to advantage be noted. The president is elected annually, but he may stand for reëlection without limitation. Sir Henry Halford, Bart., presided for twenty-four years (1820–1844). Two presidents (John Caius and Sir George Baker, Bart.) were each reëlected twice at intervals after their first presidency. The College accepts its civic responsibility by naming its Fellows to mem-

bership on many public committees and councils. The Royal College of Physicians of London is thereby a vital element in the body politic as well as the body medical of Great Britain. Nor will such a venerable institution escape the marks of its years in fixed customs and traditions. Among the most cherished of its possessions is the Gold-Headed Cane. The Trusts of the College constitute a fine legacy from the past and offer security for the future. William Harvey (June 26, 1656) gave his patrimonial estate in Kent to the College to afford the Censors a monthly collation and the Fellows an annual feast. The sums involved reflect better times. The Hamey Trust dates from Dr. Baldwin Hamey's munificence in saving the College building in Amen Corner from confiscation (1651). He made other provisions in the interest of the College; but characteristic of this institution is the preservation of the Spanish oak wainscoting of the previous building, supplied by him, to line the Censor's Room of the present home (Pall Mall East). The Sadleir Trust has an interesting history. Dr. William Croone, F.R.C.P., provided for two lectureships in his will (1684), one of which was to be delivered annually before the College. Dr. Croone afforded no support in endowment; but his widow, who later married Sir Edwin Sadleir, Bart., fulfilled her husband's design by demising the King's Head Tavern in Lambeth Hill (September 21, 1706) to her second husband for life, and, upon his death, four-fifths interest to the College of Physicians. Apparently the legacy was a profitable one, since the Sadleir Trust not only supports the Croonian Lectures, but several other less favored trusts as well. The Tavern was sold to the corporation of the City of London (1915). A study of these ancient and more recent trusts is most illuminating. The encouragement and support of research are increasingly evident in later grants and bequests. More infrequently the Royal College of Physicians is coöperative with other agencies in wide areas of human and scientific endeavor. Even the Almanac and Calendar of the College carry the reader back through its history; viz., "5 September, College House, Amen Corner, burnt down in the Great Fire, 1666," or "30 September, Harvey present for the last time, 1656." Neither devastating fire, death nor enemy bombing has submerged this proud institution.

Fate made Dr. Heinrich Stern its instrument during a visit to London in 1913. His attendance upon a meeting of the Royal College of Physicians stirred him deeply and he resolved to initiate a similar organization in America. Returning to his foster home in New York, he found little encouragement for the project. Persisting, he finally enlisted sufficient support to obtain the legal incorporation of the American College of Physicians, May 11, 1915. The first constitution defined the purposes of the American College of Physicians in these words: "To promote the advancement of the science and practice of medicine, to further the study of biological medicine among its members, to elevate the standard of preliminary education of physicians and a standard of medical education, and secure the enactment of just medical laws by the state and federal government, and of a federal

law providing for a national medical license, to attain the establishment of a national board of health, to promote friendly intercourse among physicians, to enlighten and direct public opinion in regard to great problems of health and medicine, and to afford recognition to distinguished achievement in medicine." These objectives followed in different accents the Royal College of Physicians of London's academic, administrative and medicopolitical prerogatives.

The American College of Physicians committed the first error of provincialism that had so seriously threatened the Royal College. The early Fellowship was geographically restricted to the environs of New York City. Internecine strife scarcely waited for the death of the founding spirit, Dr. Stern (May 23, 1918). The long tenure of office, which might operate advantageously or disadvantageously to the College, led to serious disaffection and was abolished (1920). With the foundation of the American College of Physicians, there was developed an associated American Congress of Internal Medicine. This organization was responsible for the conduct of the annual scientific sessions and clinics. From its rather nebulous ranks, candidates were nominated to Fellowship in the College. The Congress was administered by its own president and vice-president, but it was under the administrative control of the Council of the College. This anomalous situation was terminated by a merger of the two bodies under a revised Constitution and By-Laws in 1926.

The present Constitution of the American College of Physicians outlines its objectives as follows:

"The object of the American College of Physicians shall be to establish an organization composed of qualified internists of high standing who shall meet from time to time for the purpose of considering and discussing medical and scientific topics, and who through their organization shall attempt to accomplish the further purposes of:

"(a) Maintaining and advancing the highest possible standards in medical education, medical practice and clinical research; (b) perpetuating the history and best tradition of medicine and medical ethics, and (c) maintaining both the dignity and efficiency of Internal Medicine in its relationship to public welfare."

The academic functions of the Royal College have by time and changing circumstance been largely delegated to the medical schools of Great Britain. So well entrenched was undergraduate medical education in the United States and Canada upon the establishment of the American College of Physicians, that the conflicts with faculties of medicine, such as had marred the relationships on the Continent, and to a lesser degree in Great Britain, never arose. Yet the American College has carved for itself an important and growing responsibility for postgraduate medical education. Utilizing the facilities of the medical centers, the College has acted as a catalyst in bringing the recipient into contact with adult education. This function promises to grow steadily in effectiveness through careful planning.

The Annual Sessions of the American College of Physicians have grown in importance and significance. Not only the quality of these programs, but the continued study to improve their scope and usefulness characterizes the effort. The most recent exploration in this direction has been the introduction of television to extend the effective range of clinics and demonstrations in removed hospitals and laboratories. Perhaps most distinctive among the educational devices of the College is the Regional Meeting. From humble beginnings, these sessions have grown remarkably in strength and effectiveness. The programs, arranged by the several Governors, afford an intimate insight into the practice of a given community. No two programs are alike, but there is a studied effort to encourage the participation of the younger Associates, or prospective Associates in these communions of the spirit.

The *Annals of Internal Medicine,* as the official organ of the College, vastly extends its educational horizon. Its growth is a brief for the demand and the reception by the medical profession. Its standards have well earned its present enviable leadership among journals of like objectives. By the same token the prestige accruing to the College through its sponsorship of the Annals is an imponderable asset.

Viewed in the light of the long term investment, perhaps the most important of the College activities is its program of Research Fellowships (April 15, 1934). Many young men sustained by this support have fulfilled the promise of their earlier period, and have risen to positions of responsibility and eminence in medicine. More recent has been the embarkation of the College on the Latin-American Fellowships (March, 1949). Collaborating under a subsidy from the W. K. Kellogg Foundation, the American College of Physicians takes the responsibility for placing outstanding young teachers of Latin-American countries in appropriate clinics and medical centers in the United States. The reciprocal advantage of such interchanges cannot be overestimated. In a materialistic period of human history, even a small contribution on the scales of international amenity may well swing the balance in favor of mutual understanding and peace among nations.

Traditions are not firmly fixed in thirty-six years. The Royal College of Physicians of London, with its wealth of stimulating and colorful tradition, was almost four hundred years old when the American College of Physicians was born. Yet, there are certain straws in the wind of ultimate development in this College. To be sure, the lectureships are few, and the Trust Funds limited in number, but they are significant in their memorial origin and effective utilization. It is a healthful sign that the American College should use a considerable portion of the income of its Endowment Fund for the advancement of research. A further good prognostic index is the munificent contribution of one of its living Fellows to a Traveling Scholarship (A. B. Brower). This donation has been matched by the College for the same worthy purpose.

The founding fathers of the American College of Physicians anticipated some measure of administrative responsibility, if we may judge from the original constitution. However, the organization of American medicine in undergraduate training and licensure made such a provision presumptuous, and the later revisions of the Constitution contain no reference to such control of medical practice. However, the College has a vested interest in graduate and postgraduate medical training and continues its moral responsibility for the ethical practice of its members.

The Royal College of Physicians of London has maintained its medico-political activities at varying levels through the centuries of its existence. Its representation in important government bodies for advice and direction is an hereditary prerogative. In matters of public health, there has rarely been a dissident vote as to the propriety of its participation. Where political policy is involved, the support of the Fellowship of the Royal College has been divided. The first Constitution of the American College of Physicians clearly envisioned a parallel position of medico-political influence to that of the mother College. With the evolution of our College, this position was modified but not abrogated. The "further purpose" (of) "maintaining both the dignity and the efficiency of Internal Medicine in its relationship to public welfare" is a constitutional mandate for the participation of the College in any good work in the public weal. Traditionally, the College has remained aloof from entanglements in controversial administrative and medico-political issues. Yet, when upon due deliberation the die has been cast, the College has lent its complete support to the accepted decision. One notable example presents itself. The participation of the College in the examination of candidates for certification in internal medicine was strongly resisted as an administrative function until a careful study established its soundness and inevitability. Then the College gave not only its moral, but also its material weight to the movement, and its Fellows have contributed and will continue to contribute to the sustained growth of the American Board of Internal Medicine.

In our complex civilization new and divergent demands will perforce be made upon the American College of Physicians. The material advancement of the College has been astounding. Measured in terms of numerical strength in Fellowship, assured position in internal medicine and comparative contributions to its growth, the American College of Physicians is one of the most powerful medical organizations in the world. Nor may the College abrogate its hard-won leadership. With this position come increasing responsibilities for medical guidance in national affairs. Without a sacrifice of dignity, official representation of the College on governmental committees and councils is as desirable as it is inevitable in the fulfillment of our mission.

By careful planning for the future, we must consolidate our position. The support of research and of exchange fellowships is a most commendable

project, which should be steadily expanded. The growth of the *Annals of Internal Medicine* augurs well for the future. The Annual Sessions and the Regional Meetings are splendid efforts, but they are not enough. Mere material advantage does not suffice; the American College of Physicians of tomorrow must be a spiritual force that permeates every city, town and hamlet on this continent. In Gloucestershire late in the eighteenth century five physicians banded themselves together for social and professional interchange. Their gatherings at Fleece Inn (Rodborough) and Ship Inn (Alveston) were convivial occasions; yet from these meetings of kindred spirits came the first account of the vaccination against smallpox (Jenner), and an early association of angina pectoris with coronary atherosclerosis (Jenner; Parry). Their example is a challenge to every one of us. With the blessing of the American College of Physicians, and without stultifying protocol, small informal groups under the guidance of inspired Fellows and Associates may well bring a resurgence of clinical medicine and human service in our day.

"Make no small plans; they have no magic to stir men's souls."

OBSERVATIONS ON THE RESULTS OF SUBTOTAL ADRENALECTOMY IN THE TREATMENT OF SEVERE, OTHERWISE INTRACTABLE HYPERTENSION AND THEIR BEARING ON THE MECHANISM BY WHICH HYPERTENSION IS MAINTAINED*

By Charles C. Wolferth, M.D., F.A.C.P., William A. Jeffers, M.D., F.A.C.P., Francis D. W. Lukens, M.D., Harold A. Zintel, M.D., D.Sc.(Med.), and Joseph H. Hafkenschiel, M.D.,
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The desirability of more effective measures for the treatment of patients with severe arterial hypertension than those now available is conceded by most students of this subject. Although hypertension has been produced in experimental animals in various ways and attempts have been made to lower the levels of arterial pressure produced in these ways, such efforts as yet have neither elucidated the etiology or pathogenesis of essential hypertension, nor have they thus far led to treatment satisfactory to most observers. Nevertheless valuable leads for study of the problem have resulted. Recently much interest has developed in the possible relationships of the so-called "pituitary-adrenal axis" to clinical hypertension.

The hypotension of Addison's disease is so striking that long before development of the concept of the pituitary adrenal axis, it stimulated workers to speculate on the possible relation of the adrenal glands to hypertension. The now well established fact that when the hypertensive patient develops Addison's disease, he not only tends to lose his hypertension, but he may actually become hypotensive, suggests that under these circumstances the hypertensive mechanism fails to function because of the loss of adrenal cortical function. On the other hand, observations have been made in patients with Addison's disease which indicate that under certain conditions, they may exhibit hypertensive levels of pressure.[1, 2] Moreover, Jeffers, Lindauer and Lukens[3] found that adrenalectomy did not abolish experimentally produced "kaolin hypertension" in dogs maintained on only 1 to 3 ml. of adrenal cortical extract daily.

* Presented in abstract, Thirty-Second Annual Session of the American College of Physicians, St. Louis, Mo., April 9, 1951.

This investigation is being supported, in part, by research grants from the National Heart Institute, U. S. Public Health Service, Irwin, Neisler and Company, the Squibb Institute for Medical Research, Sandoz Pharmaceuticals and Eli Lilly and Co.

From the Edward B. Robinette Foundation, Cardiac and Hypertension Sections, Medical Clinic, Hospital of the University of Pennsylvania, the Cox Institute and the Department of Surgery, School of Medicine, University of Pennsylvania.

Various attempts have been made in the past to control hypertension by removing one adrenal gland or parts of both glands.[4, 5, 6, 7, 8, 9] Favorable results have been claimed for such procedures but the claims have not been substantiated by reports in sufficient detail to permit an accurate judgment as to what had been accomplished. Consequently about two years ago, because of the possibility that partial or subtotal adrenalectomy might be a useful procedure in the treatment of clinical hypertension, a group was organized in the Hospital of the University of Pennsylvania, with the objective of attempting to contribute to this problem. Before the project had advanced beyond the planning stage, the preliminary report by Green, Nelson and Dodds, on the early post-operative result, following almost complete bilateral adrenalectomy in a young woman with extremely severe hypertension and diabetes mellitus, was presented.[10] This encouraging report later presented in more detail [11] clearly indicated that further work should be done in the effort to discover whether or not removal of adrenal tissue deserves a place, and if so, how large a place, in the treatment of clinical hypertension.

It is not the purpose of this communication to present detailed results of work to date. Such reports are being prepared by those concerned in the various studies and will be presented elsewhere. Thus far, three preliminary reports on various aspects of the work have been presented.[12, 13, 14] The purpose here is to discuss the significance of results observed in patients following subtotal or total adrenalectomy with respect to the hypertension problem.

Our first objectives were to discover whether the blood pressure could be lowered by adrenalectomy, and if so, whether the amount of adrenal function necessary to support arterial hypertension is greater than that required to maintain a normal state of health. Because of the limitations in the treatment of adrenal cortical insufficiency at the time when this work was begun, it seemed undesirable to remove enough adrenal tissue to risk the production of Addison's disease except possibly under exceptional circumstances. When, however, cortisone became available and its value in the treatment of cortical insufficiency was established, the probability presented itself that the substitution of Addison's disease for intractable severe hypertension might prove advantageous to the patient. Prior to the availability of cortisone, the experience of Green and his co-workers [10] to the effect that a patient can be carried successfully through the post-operative period with adrenal cortical extract (ACE) was confirmed by us but the expense seemed prohibitive for routine use. With the advent of cortisone, the fear of both acute and chronic adrenal insufficiency, surgically produced, has lessened to such a degree that more radical removal of adrenal tissue could be undertaken, provided a more effective fall in blood pressure followed the more radical excisions.

The views to be expressed here are based upon observations made in 23 cases, divided as follows: (1) Eleven earlier cases subjected to subtotal adrenalectomy, of which eight have survived for periods varying from five

months to more than a year, and (2) 12 recent cases, of which 11 have thus far survived for periods of one to three months. These patients had all been refractory to medical treatment and with one possible exception the various combinations of duration of hypertension, blood pressure levels, eye ground changes, cerebral vascular resistance, cardiac deterioration and diminution of renal function, graded them as beyond the stage where good results were to be expected from any of the conventional types of sympathetic nervous system operations that have been employed in the treatment of hypertension. In the present highly experimental state of adrenalectomy, it seems proper to apply it only to patients regarded as having a poor prognosis. Moreover, if it is to gain a place in treatment, it must demonstrate its ability to bring about improvement in cardiac and/or renal function and reduce high cerebral vascular resistance.

A procedure preliminary to the present study consisted of removal in 16 cases of one adrenal gland during the second stage operation of thoraco-lumbar sympathectomy (the other adrenal gland having been ascertained to be normal in appearance at the first stage operation).[14] Although some of these patients have now been followed for nearly two years, it may still be too soon to state positively whether unilateral adrenalectomy improves the results of thoraco-lumbar sympathectomy. Perhaps it would be fair to say that the results do not seem strikingly different from those to be expected from thoraco-lumbar sympathectomy alone. Thus, the improved results reported elsewhere by the addition of unilateral adrenalectomy to sympathectomy [9] have not as yet been confirmed in this group of cases. The possibility that patients subjected to this procedure, who do not maintain satisfactorily lowered blood pressure levels may respond better to blood pressure depressing agents, such as the various drugs recently introduced for that purpose, has not yet been adequately explored by us. Thus, whether they will respond better than patients subjected to thoraco-lumbar sympathectomy alone cannot be stated at this time. None of these patients with one normal appearing adrenal gland left in situ has developed any evidence of adrenal insufficiency.

Our first case of subtotal adrenalectomy, a colored woman 33 years old, already briefly reported [13, 14] was one of the group in which thoraco-lumbar sympathectomy and unilateral adrenalectomy had been done previously. Although she had been improved by that procedure with some reduction in blood pressure, regression of eye ground changes and complete relief from attacks of paroxysmal dyspnea, the blood pressure gradually rose, although it did not attain the pre-operative levels, and she lost the postural hypotension on standing that had been present after operation. Upon re-operation, an estimated 10 per cent of the remaining adrenal gland was left in situ. Urinary corticoid excretion studies, carried out by Drs. E. M. Richardson and F. Curtis Dohan, showed that the excretion dropped from a normal level before operation, to approximately 10 per cent of the preoperative values. This patient was adequately supported in the early post-operative

stage by relatively small amounts of ACE. When cortisone became available, it was found that her blood pressure could be elevated by as little as a single intramuscular injection of 25 mg. or the daily injection of 5 to 10 mg. Postural hypotension was again present as soon as it could be tested after operation and the pressure when she was recumbent gradually fell over the course of two months to a range of 120 to 150 systolic and 90 to 110 diastolic. Later it fell still more to a range of 110 to 130 systolic and 70 to 90 diastolic, where it has remained for more than a year without any tendency to rise. After leaving the hospital she had one mild episode of adrenal cortical insufficiency lasting a few days, during a period of hot weather, when she was negligent in maintaining an adequate salt intake. During the past 10 months, she has required no supportive therapy, has been symptom free and resumed full duty in the care of her house and child. The postural hypotension has disappeared. The urinary corticoid excretion has increased to practically normal levels despite the fact that the blood pressure has remained in the normal range.

When it became apparent that the blood pressure had been strikingly lowered in this first case, the question arose as to whether the result had been due solely to subtotal adrenalectomy, or whether thoraco-lumbar sympathectomy had been an essential part of the procedure. In the effort to obtain information on this point, nine cases were subjected to subtotal adrenalectomy alone. In this group there were three deaths. One occurred six days after operation, presumably from bronchopneumonia, although in the light of later experience, it seems probable that adrenal insufficiency was also a factor, despite the maintenance of high blood pressure levels until shortly before death and relatively normal blood urea nitrogen, blood sugar, serum sodium and potassium values. Two others died a month or more after recovery from operation from recurrent cerebral vascular seizures. In two of the six patients who have survived, in both of whom an attempt was made to leave 10 per cent of one gland and 5 per cent of the other in situ, the results five and eight months after operation can be regarded as excellent. Both, however, require supportive therapy, one only about 3 mg. of cortisone daily, but the other requires 25 mg. of cortisone and 1 mg. of oral DCA, possibly due to failure of either adrenal remnant to survive. The blood pressure can be held in a normal range in both by careful regulation of treatment, but even slight increases in cortisone dosage promptly bring back hypertensive levels of pressure. Both have been completely relieved of severe congestive heart failure and no longer require cardiac treatment. One is working full time as a barber, and the other is planning to begin work soon. In a third patient with similar amounts of adrenal tissue left in situ, no supportive therapy has been required at any time, although the blood pressure, which was consistently over 200 systolic and 130 diastolic before operation, dropped to normal levels following operation, it has risen into the hypertensive range seven months later, sometimes being recorded as high as 160 to 170 systolic and 100 to 110 diastolic

when we examine him, although his own physician obtains normal figures. However, he has been completely relieved of headache which had persisted since a hemiplegic seizure six years previously. One case in which one adrenal gland was completely removed and 15 per cent of the other left in situ, had a marked post-operative fall in blood pressure and for more than two months thereafter appeared to require no supportive therapy. However, she then developed an episode of cortical insufficiency which was easily controlled. She again developed hypertension on 10 mg. of cortisone daily. This was later discontinued without return of cortical insufficiency. However, during the course of nine months, the urinary corticoid excretion has gradually risen to normal levels and the blood pressure has reverted to definitely hypertensive levels of approximately 180 systolic and 120 diastolic, figures which are still somewhat lower than her pre-operative range. In one case in which approximately 10 per cent of both adrenal glands were left in situ, the result must be classed as a failure, so far as comparison of pre-operative levels of blood pressure obtained in the hospital and those now recorded when he comes in as an ambulatory patient are concerned. However, he has gained weight and is completely relieved of severe, frequent headaches. His cerebral vascular resistance is appreciably lower, and his renal plasma flow has increased. One patient of this group, in whom 20 per cent of one adrenal gland was left in situ, must be classed as a failure in every respect. She differed from the others in that she had an abnormally high 17-ketosteroid excretion before operation and a normal excretion after operation. One accessory adrenal was found at operation and removed but the possibility remains that others not discovered are present.

It was obvious from the above that if adrenal function were sufficiently reduced, the blood pressure would fall in at least some cases However, it was equally obvious that the margin between fall of blood pressure and adrenal insufficiency may be quite narrow and that constant vigilance is necessary to maintain patients in a satisfactory state. It was apparent that none of these patients had done so well as the one with the combination of thoraco-lumbar sympathectomy and subtotal adrenalectomy.

While this part of the study was going on, a patient 57 years old, who four years before had undergone a Peet type sympathectomy, was subjected to a 90 per cent subtotal adrenalectomy. The Peet operation had not lowered his pressure and heart failure initiated by an episode of severe pulmonary edema had developed a few months prior to adrenalectomy and had required constant treatment. Following adrenalectomy, he developed only a modest fall in blood pressure in recumbency (from approximately 250–140 to 190–120) but for the first time was subject to postural hypotension. At no time did he require adrenal supportive therapy. The heart became distinctly smaller, heart failure disappeared and he has continued to feel well since operation except for nervous symptoms of long standing, which are only moderately improved. It was thought probable that had more

adrenal tissue been removed, more marked lowering of blood pressure might have been achieved.

Despite the possibility that thoraco-lumbar sympathectomy plus subtotal adrenalectomy may constitute the most effective treatment now available for severe otherwise intractable hypertension, we have hoped to avoid such a formidable program as a routine measure for dealing with advanced stages of hypertensive disease. Consequently in the next six cases, it was decided to leave in situ a small fragment of one adrenal, not exceeding 1 cm. in any diameter, section the splanchnic nerves on both sides and remove the paravertebral ganglia from T–12 to L–2 inclusive. In five of these cases, the early post-operative results have been excellent and promise well for the future. In one case, however, a 15 year old girl with a diastolic pressure usually above 170, very little fall in pressure has occurred and thus far, two months after operation, no evidences of adrenal insufficiency have made their appearance. The course of events in this case again raised the question regarding aberrantly placed adrenal tissue, although the ACTH eosinophil response test after operation was negative for evidence of cortical activity.

In two cases with extremely high blood pressure in which renal disease was far advanced, total adrenalectomy without sympathectomy has been done. Both patients have been carried through stormy post-operative courses. They have received larger amounts of supportive therapy in the early post-operative stage than cases subjected to subtotal adrenalectomy, in the effort to avoid serious adrenal insufficiency. Significant decreases in blood pressure have already been observed in these patients despite liberal dosages of cortisone and DCA. However, it remains to be decided in the future whether the progress of advanced renal disease can be arrested by adrenalectomy.

The remaining four cases have been operated on so recently that little can be said concerning three except that they survived operation and the early postoperative period without special incident. The fourth, a 47 year old man, who had been hypertensive for many years, had developed malignant change during the past six months, with progression from grade 2 retinopathy to grade 4 and rapid deterioration of renal function with a blood urea nitrogen consistently above 25 mg. per cent. Approximately 95 per cent of adrenal tissue was removed at one operation. He developed shock immediately after operation and although it was treated promptly and eventually controlled, mainly by blood transfusions, very little urine was excreted thereafter and signs suggesting cerebral ischemia developed with rapid deterioration and death a week after operation.

Discussion

Results obtained by pioneers in the field of surgery of the sympathetic nervous system, such as Adson, Peet, Smithwick, Grimson and Leriche, leave little doubt that under ordinary circumstances sympathetic nervous

system activity plays an active part in the mechanism by which hypertension is maintained. The spectacular fall in blood pressure that may develop following section of the second sympathetic chain is perhaps the most dramatic circumstance to support that view. However, the capacity of the body to compensate for the loss of sympathetic activity is such that over the course of time the blood pressure may creep back in some cases to the original level or even higher and the postural fall in pressure on standing, presumably due to pooling of blood in the splanchnic reservoir, may be lost.

The evidence available at this time, including that obtained by observations on the results of adrenalectomy in hypertensive patients, suggests that the adrenal cortex is a more fundamentally important part of the mechanism by which hypertension is maintained than is the sympathetic nervous system, i.e., loss of adrenal cortical function seems less easily compensated for than is the loss of activity produced by section of the sympathetic nervous system. Nevertheless, it appears that at least under certain circumstances, when adrenal cortical function has been lessened to such a degree that evidences of insufficiency make their appearance, a mechanism or mechanisms may function whereby hypertension can be maintained. The practical importance of learning to recognize under what circumstances such mechanisms may defeat the purposes of the operation is obvious. Most of the results that have disappointed us have occurred in patients recognized to have advanced cerebral vascular disease, but there have been exceptions to this statement for which we cannot account. Measurements of cerebral blood flow and cerebral vascular resistance which yield information of value as to the general state of the cerebral circulation cannot reflect the localization of areas where blood supply is in the most critical state. The old hypothesis that strategically located cerebral arteriosclerosis is a cause of hypertension has received little support. To speculate too far in advance of facts is not apt to be profitable. Nevertheless, the possibility that certain localizations of diminished cerebral blood supply may prevent fall in blood pressure that would occur if the blood flow were adequate, is not excluded despite the fact that cerebral vascular occlusion is sometimes followed by lower arterial pressure.

Because of the fact that arterial hypertension is readily produced by diminution of renal blood flow, it seemed probable that severe renal vascular disease might prevent a satisfactory fall in blood pressure following adrenalectomy. To what extent this may occur has not been established. It appears, however, that in most cases of hypertension, the kidneys are capable of functioning over a remarkably wide range of blood pressure, and that renal influence on blood pressure after adrenalectomy is not apt to be great. In fact, in five of six cases studied for us by Drs. J. K. Clark, A. P. Crosley and H. G. Barker [15] plasma flow through efferent vessels increased after adrenalectomy despite reductions in arterial blood pressure. Such observations are in accord with the hypothesis that the so-called renal hypertension which follows experimentally produced renal ischemia requires participation

of the adrenal cortex as a part of the mechanism by which so-called renal hypertension is maintained.

It now seems probable that adrenalectomy will have a place in the treatment of severe, otherwise intractable hypertension, until the day arrives when this stubborn malady can be controlled better by nonsurgical measures than at present. It is not certain at this time whether total or subtotal adrenalectomy will prove to be the more useful procedure. It seems not unlikely that better results will be obtained if either limited or extensive sympathectomy is combined with subtotal adrenalectomy, but if this is the case more experience will be required to determine how extensive the sympathectomy should be. The long term value of adrenalectomy in controlling hypertension is as yet unknown. There is at present at least slight evidence to suggest that adrenal regeneration may occur in humans as in experimental animals. In the long run, regeneration of a fragment left in situ may weigh heavily in favor of total adrenalectomy. Pre-operative preparation, the technic of operation including one stage versus two stage procedures, the early post-operative management and the long time care of patients who are vulnerable to all of the hazards of adrenal cortical insufficiency, all require intensive study.

The most urgent immediate need in the management of patients who have undergone adrenalectomy for hypertension is a substance with all of the properties of cortisone save for its marked blood pressure raising effect in individuals with hypertensive disease. Scarcely less important is the need for simplification of the tests now thought to be necessary to detect adrenal insufficiency in its earlier phases before sharp falls in blood pressure and the unmistakable evidences of advanced adrenal insufficiency make their appearance.

At present subtotal or total adrenalectomy should not be attempted except by fully staffed groups. First of all the group must include those competent to assess the state of the heart, kidneys and cerebral circulation, to carry out various conservative measures now applicable to the treatment of hypertensive disease, and finally, to evaluate the prospects of the patient on long term medical management. If then on the basis of such an evaluation, surgery is decided upon, someone experienced in the management of adrenal insufficiency must become a member of the group. The anesthesiologist must be familiar with the problems involved in maintaining satisfactory blood pressure levels in hypertensives during operation, and at the same time avoiding serious heart failure in those already on the verge of that condition. The importance of rapid careful operation, with knowledge on the part of the surgical team of the technical problems and emphasis on avoidance of shock, goes without saying. The early post-operative management involves problems of fluid intake, urinary output, maintenance of satisfactory electrolyte patterns, preservation of adequate cardiac function and avoidance if possible of dangerous adrenal insufficiency, or at least its early recognition and prompt treatment. Later the problems become those

of close supervision of patients, the necessity in some of adjusting cortisone, DCA and salt administration, to find the combinations that will best maintain adequate adrenal function and at the same time avoid undesirably high blood pressure. The cardiac and renal status must not be neglected. It is desirable to have studies at appropriate intervals of the eye grounds, cerebral blood flow, and cerebral vascular resistance, excretion of urinary corticoids and 17-ketosteroids, electrocardiogram and orthodiagram, glomerular filtration rate and renal plasma flow, blood sugar, blood urea nitrogen, serum sodium and potassium, in order to evaluate the progress of patients. Such a program obviously requires the collaboration of workers in various fields, although doubtless in time the program of management can be simplified to a considerable degree.

If the studies now in progress establish the fact that the combination of adrenalectomy and sympathectomy achieve better results in controlling hypertension and restoring patients to an improved state of health than either procedure alone, an important step will have been taken in the direction of the eventual medical management of hypertensive disease. It will indicate the need for determining whether medical treatment, in order to be most effective, must be directed both toward control of sympathetic nervous system activity and depression of adrenal cortical function. It is therefore important that concurrently with studies of the merit of surgical procedures, intensive investigation be continued to discover more effective nonsurgical agents, which either singly or in combination improve the control of hypertension.

Summary

Studies have been undertaken in an effort to discover whether adrenalectomy deserves a place in the treatment of hypertensive disease and if so, under what conditions it will prove useful. As a first step 16 patients were subjected to unilateral adrenalectomy in connection with the second stage of the Smithwick type thoraco-lumbar sympathectomy. The results, contrary to those of previous reports, did not appear to be superior to those anticipated from the thoraco-lumbar operation alone. The next step included more radical excision of adrenal tissue ranging in 23 cases from the removal of approximately 90 per cent to complete adrenalectomy. In 15 cases the operation was limited to adrenalectomy and in eight it was combined with either limited or extensive sympathectomy.

The arterial blood pressure has been reduced in some cases from extremely high levels to a normal range by subtotal adrenalectomy alone with marked symptomatic improvement, relief from heart failure, improvement in renal plasma flow and reduction in cerebral vascular resistance. In order to achieve such results, it has been necessary to remove more than 90 per cent of adrenal tissue and create a grade of adrenal cortical insufficiency requiring at least minimal replacement therapy.

The combination of subtotal adrenalectomy and sympathectomy has yielded more promising results than adrenalectomy alone, although many more cases and longer periods of observation will be required to warrant a conclusion. In one patient among the original group of 16 subjected to bilateral thoraco-lumbar sympathectomy and unilateral adrenalectomy in whom that operation had failed to control severe hypertension, the blood pressure has been maintained in a low normal range for over a year following the removal of approximately 90 per cent of the remaining adrenal gland. In five of six cases in which the removal of at least 95 per cent of adrenal tissue was combined with bilateral splanchnicectomy and bilateral sympathectomy T–12 to L–2 inclusive, the early post-operative fall in pressure has tended to be more satisfactory than that obtained from adrenalectomy alone.

If the combination of subtotal adrenalectomy and sympathectomy proves to be the most effective surgical attack on hypertension, its most effective control by nonsurgical methods may require the combination of depression of adrenal cortical function and sympathetic nervous system activity.

ACKNOWLEDGMENTS

Dr. William T. Fitts performed the operation of subtotal adrenalectomy in two of the cases included in this report and directed the surgical aspects of post-operative care.

Dr. David P. McCallie has aided in the study and treatment of patients.

Miss Nelly Jane Keffer has made daily blood pressure readings when patients were in the hospital, including postural tests whenever possible. She has helped prepare various tables.

Generous supplies of adrenal cortical extract have been furnished by the Upjohn Company.

Merck and Company, Inc. has supplied the large amounts of aqueous suspension and tablets of Cortone, used in this study.

Ciba Company has furnished DCA for both oral and parenteral use.

The Schering Company has furnished DCA for both oral and parenteral use.

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THE EFFECTS OF PRISCOL (2-BENZYL-4, 5-IMIDAZOLINE HYDROCHLORIDE) IN THE TREATMENT OF PERIPHERAL VASCULAR DISEASES *

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IT is the purpose of this paper to report the clinical results obtained with a new vasodilator, 2-benzyl-4, 5-imidazoline hydrochloride (Priscoline), in the treatment of 22 patients with various types of peripheral vascular disorders. In the past few years several new drugs have been added to the therapeutic armamentarium of peripheral vascular disease; these are: diethyl ether, histidine and ascorbic acid, vitamin E, dibenamine, tetraethyl ammonium and Priscoline.† We at the Jersey City Medical Center have had some experience with the last three drugs.

The use of diethyl ether was reported by Katz [1] in 1946. He administered the drug in a 2.5 per cent solution of 5 per cent glucose in distilled water to a group of patients with diabetic arteriosclerosis obliterans. The solution had to be refrigerated because of its explosive potentialities. It was given slowly and repeated daily for 12 days. He reported marked relief of ischemia and pain. Eighty per cent of the patients treated for impending gangrene were saved from amputation. It was also tried with favorable effects in a few patients with nondiabetic arteriosclerosis obliterans, Raynaud's syndrome, thromboangiitis obliterans and other angiospastic states. He was unable to explain the mechanism of action of this drug. Lichtenstein and Sewell [2] reported the death of a 75 year old patient during the course of an infusion with diethyl ether. Autopsy revealed definite pulmonary and cerebral fat embolism. Wirtschafter and Widmann [3] noted the development of gross hematuria and jaundice in a small series of patients that they treated by this method.

Wirtschafter and Widmann felt that the beneficial effects of diethyl ether were attributable to the release of histamine. They then recalled the work of Holtz,[4] who reported the conversion of histidine to histamine in vitro by the action of ascorbic acid. Their method was as follows: Patients were first given 500 mg. of sodium ascorbate intravenously. This was followed by the intramuscular injection of 5 c.c. of a 4 per cent aqueous solution of histidine monohydrochloride simultaneously with the subcutaneous injection of 100 mg. of sodium ascorbate. This procedure was repeated at four to 12

* Received for publication May 30, 1949.

From the Medical Service and Peripheral Vascular Clinic of the Jersey City Medical Center.

† Formerly marketed by the Ciba Company under the name of Priscol.

hour intervals, depending on the severity of the clinical findings. In addition, patients received 600 mg. of ascorbic acid orally daily. Eleven cases of peripheral vascular disease were treated. All responded favorably, and none required amputation. The degree of improvement was judged solely by clinical observations. No laboratory studies were done to determine changes in the circulation. Friedell, Drucker and Pickett [5] treated 25 patients with arteriosclerosis obliterans by this method. These patients had previously failed to respond to other conservative measures. The majority of the cases responded favorably to this regimen in terms of clinical improvement. However, the usual tests for determining blood flow failed to show any appreciable changes.

Allen of the Mayo Clinic, at the 1947 meeting of the American College of Physicians, stated that this form of therapy had been found to be of no value by him and his coworkers.

A new development in histamine therapy has recently been reported by Mufson.[6] This treatment consists of weekly and biweekly intraarterial infusions of histamine. The technic is quite simple. He has given over 500 such injections without mishap. His circulatory studies consisted of skin temperature determinations, oscillometric readings and estimations of the diffusion of radioactive sodium. These tests seemed to indicate definite dilatation of the entire vascular tree of the treated limb. The effect of an injection could be demonstrated for as long as six hours. However, the clinical results showed cumulative and mounting improvement from weekly and biweekly treatments. Walking tolerance was greatly benefited in 85 per cent of the patients. Sleep pain was relieved in all cases. Relief was noted after three to six treatments.

Shute [7] and his coworkers reported remarkable results in indolent varicose ulcers, thrombophlebitis, early gangrene of the extremities and thromboangiitis obliterans after the administration of α-tocopherol. They had similar astonishing results in coronary, hypertensive and rheumatic heart disease and in cerebral thrombosis. Their findings are based on clinical observations. Vitamin E has not been shown by pharmacologic tests to have vasodilating action. In our hands and in those of several other observers, it has been found to be entirely inert.

Dibenamine was originally described by Eisleb in 1930 and later prepared in this country by Gump. Its pharmacology was first reported by Nickerson and Goodman.[9] Dibenamine is N, N-dibenzy-β-chloroethylamine. It structurally resembles the nitrogen mustard gases. The intravenous route is the only effective mode of administration. In physiologic doses, dibenamine is an effective adrenergic blocking agent. The blocking action upon the responses to sympathetic nerve stimulation develops more slowly and less completely than its blocking action upon the responses to adrenalin. The effects of a single injection last 36 to 96 hours. Resting blood pressure, heart rate and the electrocardiogram in normotensive individuals are not significantly altered. Orthostatic hypotension occurs in

both normotensive and hypertensive patients and can be elicited for 12 to 24 hours after administration of the drug. Postural tachycardia persists even longer. It increases the blood flow and elevates skin temperatures, particularly in patients with neurogenic vascular spasm of the extremities. On the basis of its pharmacologic actions, dibenamine and its congeners should be of value in conditions in which partial or complete blockade of excitatory adrenergic functions is indicated for diagnostic or therapeutic purposes. These conditions, to mention only the more obvious, would include peripheral vascular diseases such as thrombophlebitis, acute arterial occlusion, frostbite, causalgia, Raynaud's disease and organic vascular insufficiency with components of functional spasm. However, Hecht [10] and his group at the University of Utah studied 70 patients and found that this drug caused severe toxic reactions in almost all their patients. The consensus among the majority of investigators of this agent is that dibenamine in safe doses is a valuable pharmacologic tool but that it appears to have limited therapeutic possibilities.

Tetraethyl ammonium has been known for years. Its vasodepressor action had been observed many years ago by Marshall, Pritchard and Trendelenburg. Acheson and Moe [11] and Acheson and Pereira [12] in 1946 brought it again to the attention of the medical profession. By animal experimentation, they conclusively demonstrated that the drug exerted its effects by blocking the ganglion in the efferent pathways of the sympathetic and parasympathetic nerves. Berry [13] reported that tetraethyl ammonium caused a rise in skin temperature in man equal to or greater than that caused by sympathetic block. Slaughter [14] claimed that it increased the blood flow in the upper extremities 100 per cent and in the lower extremities 135 per cent in a group of normal persons. These observations were based on plethysmographic studies. In 1946, Lyons and coworkers [15] issued a very promising report. Their results were favorable in thromboangiitis obliterans, thrombophlebitis with evidence of vasospasm, causalgia, Raynaud's disease, acrocyanosis, pernio and other vasospastic states. The drug was administered either intravenously or intramuscularly. They felt that the drug produced an autonomic blockade as efficient as that obtained by sympathetic block. In arteriosclerosis obliterans it helped control nocturnal pain. In a later report,[15] these same investigators felt that they were overly enthusiastic about their results. However, they still contended that tetraethyl ammonium was a valuable diagnostic aid but did not replace sympathectomy for therapy. DeBakey [16] and Pearl [17] independently found that local nerve and regional sympathetic block invariably produced an increase in the skin temperature from two to six times greater than the increase caused by tetraethyl ammonium. Of particular significance is the fact that local nerve and regional sympathetic block always resulted in an increase in skin areas which had failed to respond to the use of the drug. Finally, the duration of elevation following block was in every instance considerably more prolonged than the rise following the administration of tetraethyl am-

monium. They concluded that tetraethyl ammonium was of no value therapeutically and diagnostically. This coincides with our own impression. Besides, it has many undesirable side reactions. Friedlick [18] reported a case in which the patient went into a prolonged shocklike state following the intravenous injection of 230 mg. of tetraethyl ammonium. One death [19] has been reported to date which could be attributed to this medication.

Priscoline was first reported by Hartmann and Isler [20] in 1939 as a possible agent in the treatment of hypertension. At approximately the same time, Meier and Müller [21] demonstrated the vasodilatory action of Priscoline, stating that it was more pronounced in the extremities. They were the first to demonstrate that Priscoline and adrenalin, given together, produced lowering of the blood pressure. Meyer,[22] in 1941, proved the adrenolytic properties of Priscoline. In 1947, Ahlquist, Huggins and Woodbury [23] reported that Priscoline produced peripheral vasodilatation, increased cardiac output, and some inhibition of the gastrointestinal musculature. Occasional elevations of blood pressure are ascribed to increased cardiac output over peripheral vasodilatation. Hatt,[24] using the Starling heart-lung preparation, demonstrated that damaging doses of Priscoline were 100 times greater than those used to reduce blood pressure. Grimson, Reardon, Marzoni and Hendrix,[25] in a recent study conducted at Duke University, confirm the reports of the South American and European investigators. They found that, with few exceptions, single doses of 50 to 75 mg. produced changes in the circulation of limbs equivalent to those produced by sympathetic block or sympathectomy. Continuing treatment with these doses maintains benefit but does not entirely equal the effect of sympathectomy. Results in Raynaud's disease have been so encouraging that sympathectomy is no longer utilized. Results in causalgia and other vasospastic states showed the drug is of definite value. In arteriosclerosis and thromboangiitis obliterans the results were not so striking but were definitely encouraging. They did not observe any deleterious effects of the above doses on co-existing coronary artery disease. Oscillometric readings were unchanged in marked arterial occlusive disease and improved in cases with mild or moderate involvement. Postural hypotension occurred after the administration of very large doses. They felt that the drug has a definite adrenalin blocking action in view of its action on sympathectomized limbs.

This report deals with the results of a clinical investigation of Priscoline in the treatment of various peripheral vascular disorders over a period of approximately 22 months.

Procedure

Patients for study were referred to the peripheral vascular disease clinic of the Jersey City Medical Center. Each available room contained six examining tables. Each patient was allowed to rest for one hour before studies were started. Room temperatures fluctuated slightly. Complete physical examination was supplemented by oscillometric readings of the

lower extremities at the foot, ankle, calf and thigh, and temperature readings of each of the toes and of the dorsum of the foot. Laboratory studies included urinalysis, complete blood count, blood sugar, blood non-protein-nitrogen, Wassermann reaction, electrocardiogram and soft tissue roentgenogram of the lower extremities. Gastrointestinal studies were done on two cases. Patients were seen weekly for two months, and then every two weeks thereafter. Patients who were incapacitated were hospitalized, and treatment with Priscoline was regulated by one of us. In order to determine the distance a patient could walk after therapy, a circle 30 yards in circumference was mapped out. The patients were permitted to walk this circle until the beginning of pain in the calf. If the patient walked one mile without pain he was permitted to stop. Because many of the patients were started on therapy before a walking test could be done, it was necessary to approximate the distance the patient could walk prior to therapy according to his own history, the average block measuring 80 yards. On discharge, the patient was referred to the peripheral vascular disease clinic for follow-up care. All patients were coöperative and at the present time are still being followed.

Material

A total of 22 patients was studied in whom the following disease entities were exhibited: peripheral arteriosclerosis, 15; arteriosclerotic heart disease, seven; hypertension, eight; hypertensive heart disease, three; thromboangiitis obliterans, three; diabetes, two; anginal syndrome, one; frostbite, one; rheumatic heart disease, one; lues, one; duodenal ulcer, three; Raynaud's disease, one; coronary artery disease, seven. Eleven cases exhibited definite calcification of the peripheral vessels, four cases had ulcerations of the fingers or toes, and three cases had already had amputations performed. One case of coronary artery disease with infarction exhibited signs and symptoms interpreted as saddle thrombus.

The youngest patient treated was 29 years of age, the eldest 75, the average age being 56.7 years. Those with thromboangiitis obliterans ranged from 29 to 44 years, the average being 39. Those with arteriosclerosis ranged from 51 to 75 years, the average being 62.

Two males who exhibited no evidence of peripheral vascular disease were used as controls. They were 24 and 53 years of age, respectively.

The following case reports are representative of the group studied.

Case Reports

Case 1. Control No. 1. A young male, 24 years of age, with no evidence of disease, was given 50 mg. of Priscoline intramuscularly. Figure 1 reveals, in graph form, the response recorded hourly. Each determination represents the average temperature of the five toes of each foot.

Case 2. Control No. 2. A male, aged 53, with no evidence of disease, was given 50 mg. of Priscoline intravenously. Figure 2 reveals the response recorded hourly.

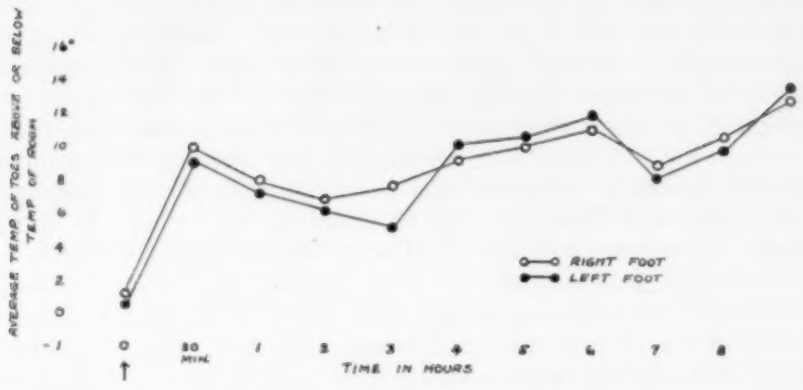

FIG. 1. Control No. 1, male, age 24, response to Priscol 50 mg. intramuscularly.

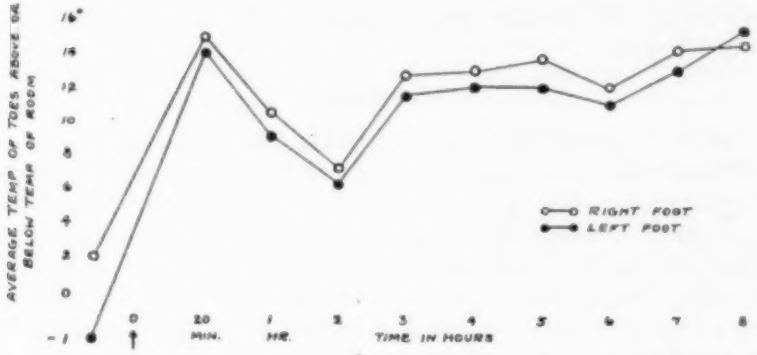

FIG. 2. Control No. 2, male, age 53, response to Priscol 50 mg. intravenously.

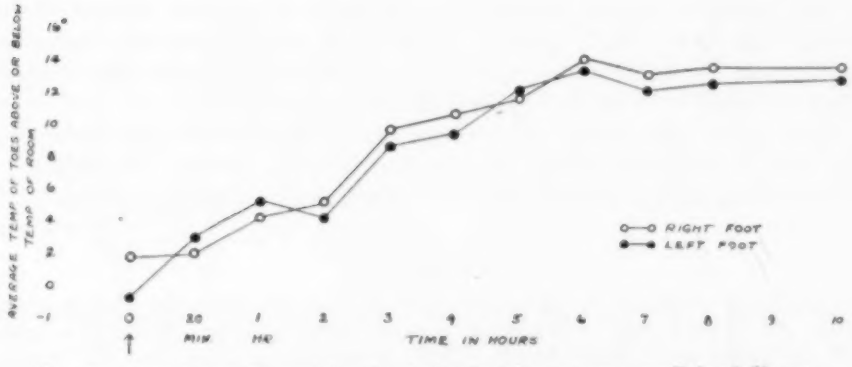

FIG. 3. Case 1, age 65, peripheral arteriosclerosis; response to Priscol 50 mg. intramuscularly.

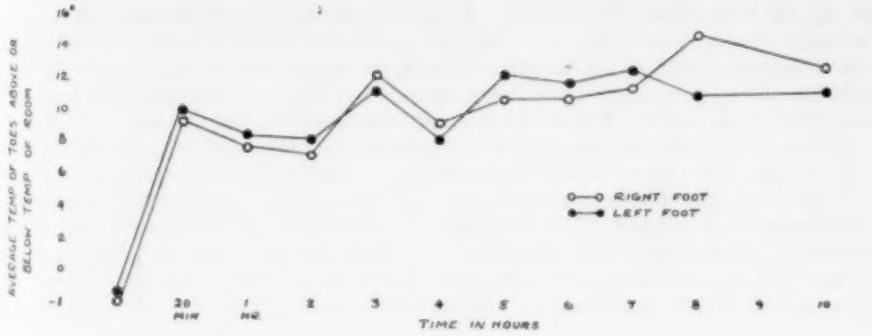

FIG. 4. Case 2, male, age 59, peripheral arteriosclerosis; response to Priscol 50 mg. intravenously.

Case 3. Figures 3 and 4 represent the responses of two patients, aged 65 and 59, respectively, with definite peripheral vascular disease, who were given 50 mg. of Priscoline intramuscularly and intravenously, respectively.

As illustrated by the graphs, there is a gratifying response noted in both control and pathologic cases, intravenous administration causing an abrupt rise in temperature while intramuscular administration causes a gradual but steady rise. All responses were sustained over a period of nine or 10 hours, at which time the patients requested that the studies be discontinued.

Case 4. A 61 year old male patient with diabetes mellitus, arteriosclerotic heart disease and peripheral arteriosclerosis on treatment with oral Priscoline was given

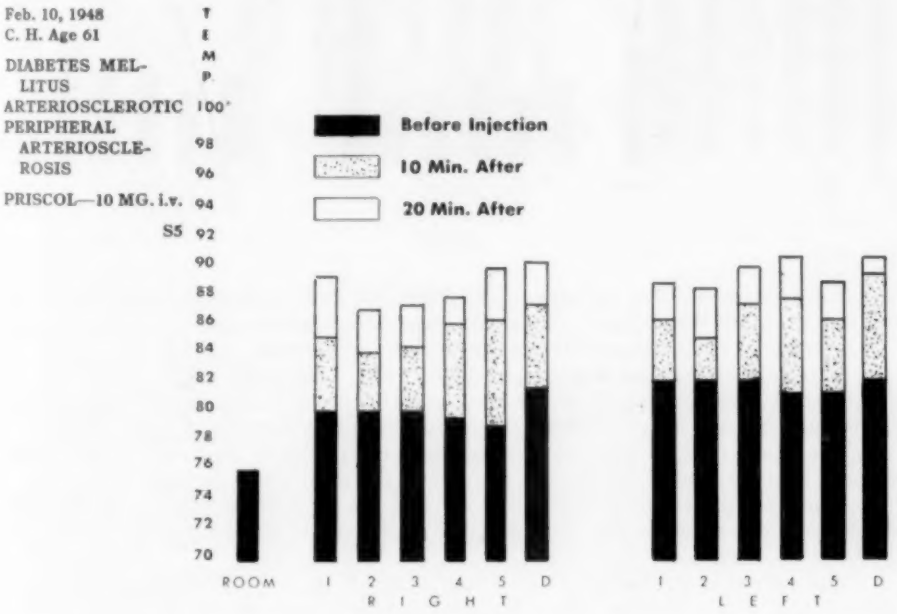

FIG. 5.

10 mg. of Priscoline intravenously. Temperature readings of the toes taken before injection averaged four degrees above the temperature of the room. In 10 minutes the temperature readings averaged nine degrees above that of the room, and in 20 minutes, 12 degrees above that of the room. The improvement was still evident at the end of four hours. Figure 5 represents this study in graph form.

Case 5. A 62 year old male boiler tender was first seen on December 2, 1947. For the past three years he had had intermittent claudication after walking one block.

Physical examination revealed cold feet with pallor. The dorsalis pedis pulsations were not palpable. The blood pressure was 138 mm. Hg systolic and 80 mm. diastolic. Laboratory examinations of the blood and urine were all within normal limits. Electrocardiogram revealed cor pulmonale. Roentgenogram of the legs revealed no obvious calcification. Oscillometric readings for the foot, ankle and calf

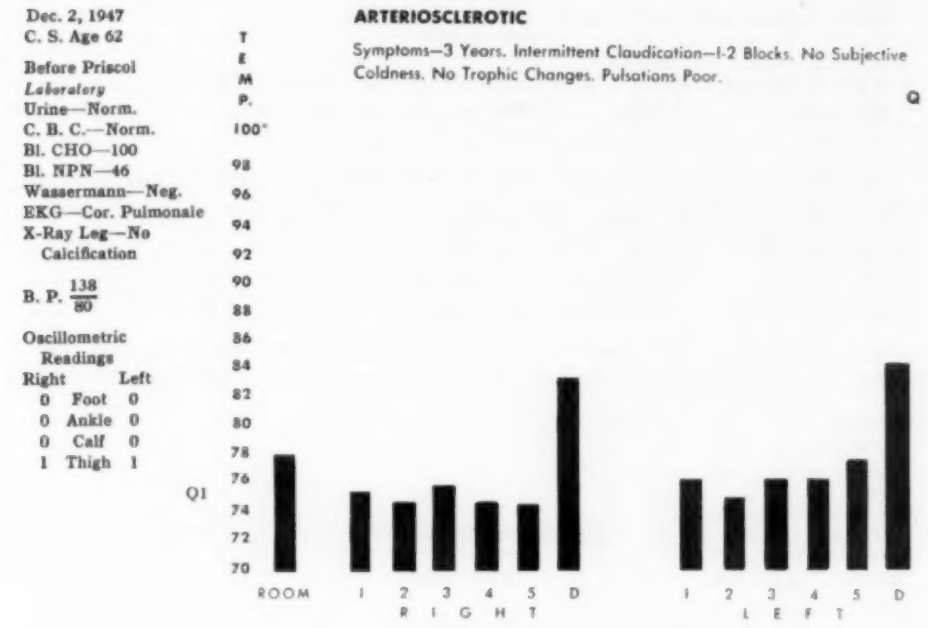

FIG. 6.

were zero for both sides, and one at the thigh for both sides. The temperature of the toes averaged three degrees below the temperature of the room.

Diagnosis: Peripheral arteriosclerosis and cor pulmonale.

Treatment: Priscoline was given orally, 25 mg. four times a day.

Result: Three weeks later, the temperature of the toes averaged two degrees above that of the room. The feet were warm and the patient could walk one mile.

One month after therapy was started, the temperature of the toes averaged seven degrees above that of the room, and the patient could walk any distance.

Two months after the institution of therapy, the temperature of the toes averaged 13 degrees above that of the room and now pulsations of the dorsalis pedis could be palpated on both sides.

The patient is still being followed and, although he discontinued medication four months ago, is still asymptomatic. Repeat laboratory examinations reveal no change from the original.

Before taking Priscoline, the patient could walk only 80 yards. On December 7, 1948, he was able to walk 900 yards.

Figures 6 and 7 represent in graph form the studies before and after the administration of Priscoline.

Case 6. This 54 year old male salesman, first seen on May 7, 1948, had had cold feet for the past two years and intermittent claudication after walking one-half block.

Physical examination revealed cold feet, rubor on dependence and pallor on elevation. Dorsalis pedis pulsations were not palpable. The blood pressure was 120 mm. Hg systolic and 75 mm. diastolic. The patient stated he had had a duodenal ulcer at 34 years of age. Laboratory examinations of the blood and urine were within normal limits. Roentgenogram of the legs revealed calcification to be present.

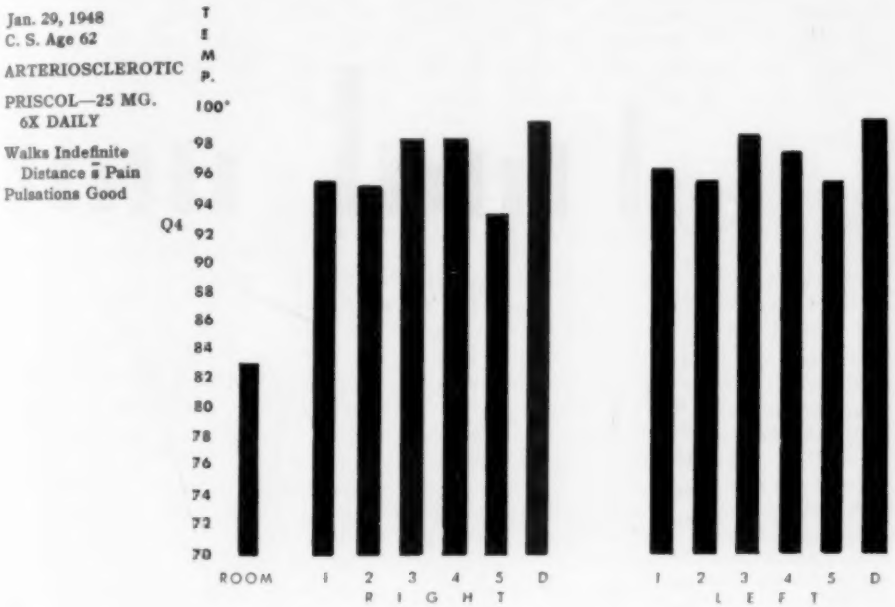

FIG. 7.

Oscillometric readings were zero throughout on both sides. The temperature of the toes averaged four degrees below the room temperature.

Diagnosis: Peripheral arteriosclerosis.

Treatment: The patient was put on Priscoline, 50 mg. orally four times a day.

Results: One month later, the temperature of the toes averaged 10 degrees above the temperature of the room. The patient felt much better. His feet were warm and had a good color. He could walk six blocks without pain. However, he began to complain of epigastric pain following the administration of Priscoline. Gastrointestinal series revealed an active duodenal ulcer. This was treated while he continued to take Priscoline and he became asymptomatic.

Two months after treatment was instituted, the temperature of his toes averaged 11 degrees above that of the room and he could walk any distance. Repeated laboratory examinations have remained normal.

May 7, 1948
H. V. Age 54

Before Priscol
Laboratory
Urine—Norm.
C. B. C.—Norm.
Wassermann—Neg.
Bl. NPN—32
Bl. CHO—110
EKG—Left Axis Dev.
X-Ray Legs—
Calcification
Present

B. P. $\frac{125}{75}$

Oscillometric
Readings
Right Left
0 Foot 0
0 Ankle 0
0 Calf 0
0 Thigh 0

PERIPHERAL ARTERIOSCLEROSIS.

Symptoms—2 Years. Intermittent Claudication—½ Block.
Cold Feet. Rubor on Dependence. Pallor on Elevation No Pulsations
Palpable. Duodenal Ulcer at 34.

C

T
E
M
P.
100°
98
96
94
92
90
88
86
84
82
80
78
76
74
72
70
C1

FIG. 8.

June 6, 1948
H. V. Age 54

PERIPHERAL
ARTERIOSCLE-
ROSIS

PRISCOL—50 MG.
4X DAILY

Feet Feel Fine
Walks 6 Blocks s Pain
Feet Warm and Good
Color
Epigastric Pain—
Duod. Ulcer

B. P. $\frac{120}{70}$

T
E
M
P.
100°
98
96
94
92
90
88
86
84
82
80
78
76
74
72
70
C1

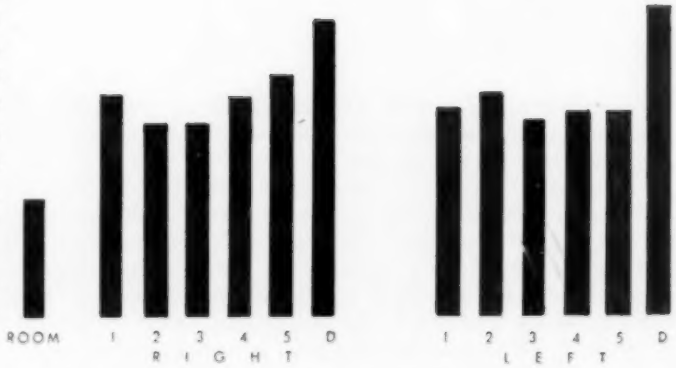

FIG. 9.

Before taking Priscoline, the patient could walk only 40 yards. On November 30, 1948, he was able to walk one mile without pain.

Figures 8 and 9 represent in graph form the studies before and after the administration of Priscoline.

Case 7. A 69 year old female with arteriosclerotic heart disease with a recent posterior wall infarction and paroxysmal auricular fibrillation was suddenly seized with severe pain in the left thigh and groin, coldness, blanching, and then cyanosis of both feet and legs. The feet and legs, according to the patient, became "dead." She stated the left was more involved than the right. Two consulting physicians diagnosed a saddle thrombus. Examination revealed cold, cyanotic feet and legs with dorsalis pedis, popliteal and femoral pulsations absent on both sides. Priscoline, 30 mg. intravenously, was given every four hours day and night. Within 24 hours definite improvement was noted in both feet and legs. The feet were warm and of good color, and the patient stated she could feel them becoming alive again. After five days of treatment the feet and legs felt perfectly normal to the patient. The right femoral was palpable, and two examiners stated that the right popliteal pulsation was palpable. At this writing she is still on Priscoline but is taking it orally, 50 mg. every four hours. She has complained only of slight gastric distress. Her feet and legs remain improved. On the basis of results achieved, it is probable that she had an embolus or a thrombus on the left side with resultant widespread vasospasm.

Case 8. This 44 year old male policeman was first seen on March 16, 1948. For the past three years he had had intermittent claudication after walking one-quarter of a block, and pain at rest.

Physical examination revealed the left leg amputated (one year); gangrene of four toes of the right foot, with edema, inflammation, infection and severe pain; ulcerations of two fingers of the right hand, and two fingers of the left hand. The blood pressure was 128 mm. Hg systolic and 78 mm. diastolic. Dorsalis pedis pulsations were not palpable. Laboratory examinations of the blood and urine were all within normal limits. Roentgenogram of the leg revealed no calcification. Oscillometric readings were zero for the foot and ankle, and one-half for the calf and thigh. The temperature of the toes averaged 1.4 degrees above that of the room.

Diagnosis: Thromboangiitis obliterans.

Treatment: The patient was hospitalized and Priscoline was given intravenously, beginning at 10 mg. three times a day and increasing 10 mg. three times a day, until the patient was receiving 50 mg. three times a day.

Results: One month later, the temperature of the toes averaged eight degrees above that of the room, the foot looked better, the redness, edema and pain were gone, the area of necrosis was smaller, and the fingers were completely healed.

Two months after institution of therapy the temperature of the toes averaged seven degrees above that of the room, and the area of necrosis was markedly reduced in size.

Three months after beginning therapy, the temperature of the toes averaged seven degrees above that of the room and all toes were healed except the great toe.

Treatment has been continued to the present, at which time only a small area of necrosis remains at the tip of the great toe. The patient is able to stand on his foot for one hour or more without discomfort. Repeated laboratory examinations reveal no deviation from the normal values obtained originally.

Figures 10 and 11 represent in graph form the studies before and after the administration of Priscoline.

Case 9. This 29 year old male machinist was first seen on February 17, 1948. For the past two years he had had intermittent claudication on walking two blocks.

Physical examination revealed cold feet, moderately cyanotic. The dorsalis pedis pulsations were not palpable. The blood pressure was 128 mm. Hg systolic and

Mar. 16, 1948
J. H. Age 44

Before Priscol
Laboratory
Urine—Norm.
C. B. C.—Norm.
Wassermann—Neg.
Bl. NPN—22
Bl. CHO—73
EKG—Norm.
X-Ray Leg—No Calcification

B. P. $\frac{128}{78}$

Oscillometric Reading

Right	Left
0	Foot ampt.
0	Ankle ampt.
½	Calf ampt.
½	Thigh ampt.

L1

T
E
M
P.
100°
98
96
94
92
90
88
86
84
82
80
78
76
74
72
70

ROOM.

THROMBOANGIITIS OBLITERANS.

Symptoms—3 Years. Intermittent Claudication—¼ Block
Pain at Rest. Left Leg Amputated. Right Foot—4 Toes.
Right Hand—2 Fingers. Left Hand—2 Fingers. Gangrene Ulceration.
Right Leg—Edematous—Inflamed—Infected—Painful.

L

FIG. 10.

Apr. 12, 1948
J. H. Age 44

THROMBOANGIITIS OBLITERANS

PRISCOL—40 MG. T.I.D. I.V.

Foot Looks Better
Redness Gone
No Pain or Edema
Area Necrosis Smaller
Fingers Healed

B. P. $\frac{130}{80}$

L2

T
E
M
P.
100°
98
96
94
92
90
88
86
84
82
80
78
76
74
72
70

ROOM

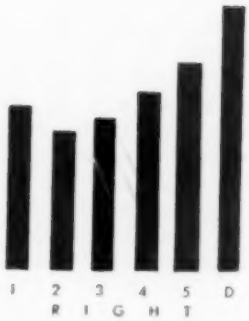

FIG. 11.

75 mm. diastolic. Laboratory examinations of the blood and urine were all within normal limits. Roentgenogram of the legs revealed no calcification. Oscillometric readings were zero for the foot and ankle on both sides, a trace for the calf on both sides, and one for the thigh on both sides. Temperature studies were not done until the patient had been treated for one week.

Diagnosis: Thromboangiitis obliterans.

Treatment: The patient was put on Priscoline, 50 mg. orally four times a day.

Results: One week later, the temperature of the toes averaged two degrees above that of the room.

Six weeks after therapy was instituted, the temperature of the toes averaged 10 degrees above that of the room, but he still could walk only two blocks.

Two and one-half months after beginning treatment the temperature of the toes averaged 10 degrees above the room temperature and he could walk six blocks without pain.

Three months after institution of treatment, the temperature of the toes averaged 12 degrees above that of the room and he could walk 24 blocks with a minimum of pain.

He has been followed to the present and is asymptomatic. Repeated laboratory examinations remain normal. He now receives Priscoline, 50 mg. five times a day.

Before taking Priscoline, the patient could walk only 160 yards. On November 30, 1948, he was able to walk 700 yards.

Figures 12 and 13 represent in graph form the studies before and after the administration of Priscoline.

Case 10. This 54 year old male clerk, first seen on May 18, 1948, gave a history of having had for the past five months a cold painful left index finger with ulceration, noted after working in severe snow storm for an extended period of time.

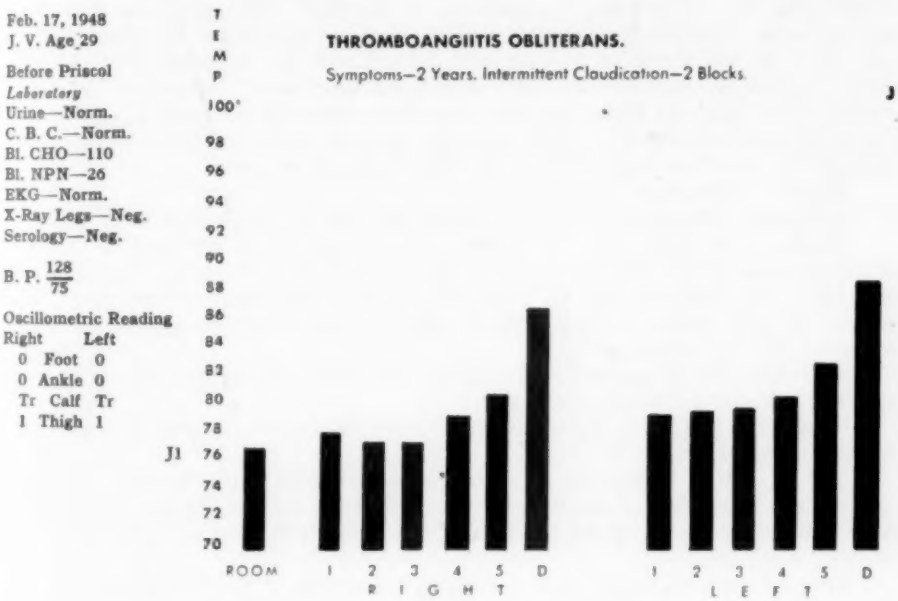

FIG. 12.

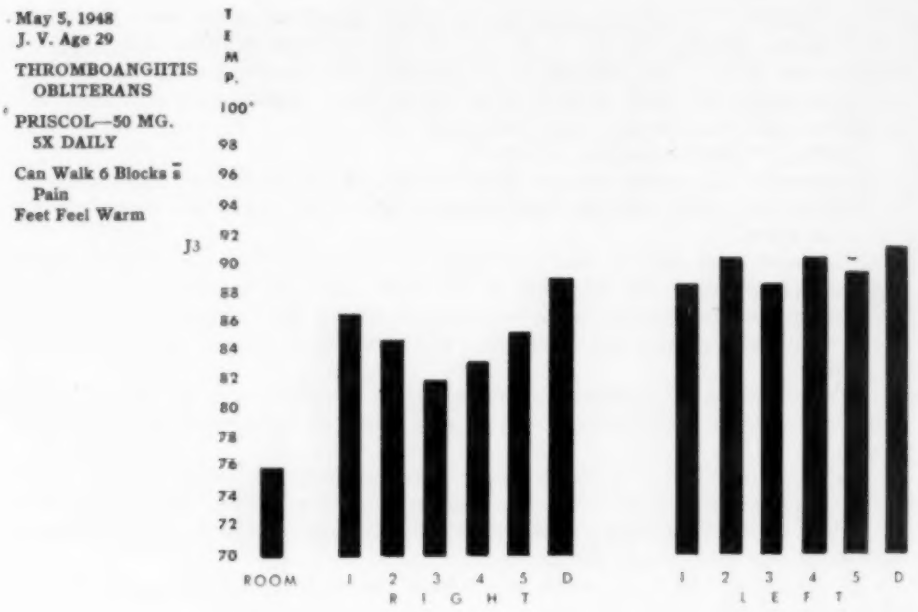

FIG. 13.

Physical examination revealed that the left index finger was very cold, cyanotic, and painful to touch and motion, with ulceration about 1 cm. in diameter on the inner aspect of the proximal phalanx. The blood pressure was 128 mm. Hg systolic and 75 mm. diastolic. Laboratory examinations of the blood and urine were all within normal limits. Oscillometric readings of the legs were zero for the foot on both sides. On the left, the ankle was one-half, the calf five, and the thigh four. On the right, the ankle was one-half, the calf four, and the thigh two. Temperature readings of the fingers averaged 12 degrees above the temperature of the room for all fingers except the left index finger, which was the same as the temperature of the room. The toes averaged one degree below the temperature of the room.

Diagnosis: Frostbite.

Treatment: The patient was put on Priscoline, 50 mg. orally four times a day.

Results: One week later, the temperature of the fingers averaged 20 degrees above the room temperature, and the left index finger was 11 degrees above that of the room. The toes averaged 17 degrees above the temperature of the room. The patient felt much better. The left index finger was pink and less painful and could be moved without causing pain.

At present, the ulceration is completely healed and the patient uses his finger normally without discomfort of any sort.

Figures 14 and 15 represent in graph form the studies before and after the administration of Priscoline.

Case 11. This 38 year old male bus driver, first seen on October 17, 1948, had for the past month had a severe cyanosis of the terminal and second phalanges of the middle three fingers of the right hand, associated with pain and spinal pain for the past two years.

Physical examination revealed a cyanotic appearance of the two distal phalanges of the middle three fingers of the right hand, with multiple small petechiae scattered throughout. There were ulceration and desquamation of the superficial skin, with

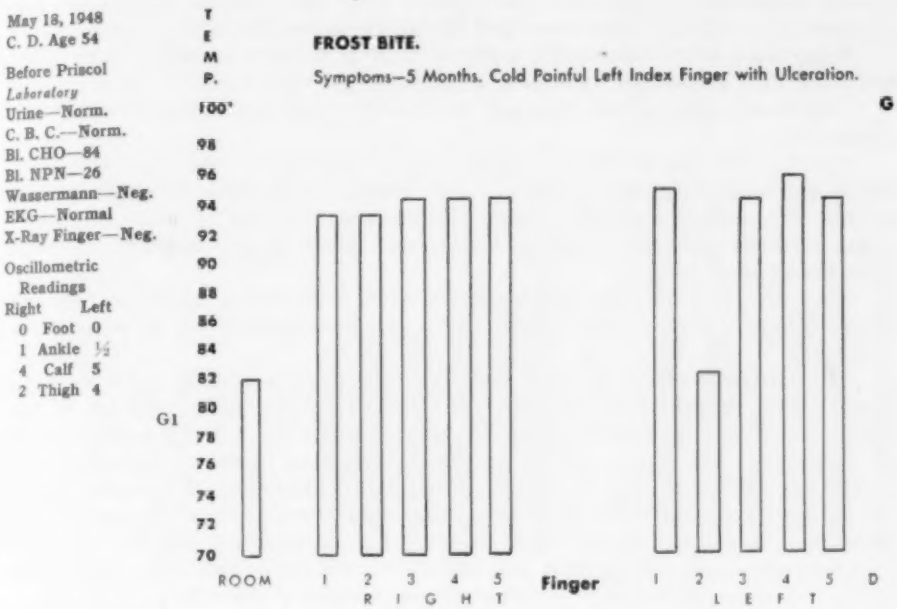
May 18, 1948
C. D. Age 54
Before Priscol
Laboratory
Urine—Norm.
C. B. C.—Norm.
Bl. CHO—84
Bl. NPN—26
Wassermann—Neg.
EKG—Normal
X-Ray Finger—Neg.
Oscillometric Readings
Right Left
0 Foot 0
1 Ankle ½
4 Calf 5
2 Thigh 4
G1
TEMP.
100°
98
96
94
92
90
88
86
84
82
80
78
76
74
72
70
FROST BITE.
Symptoms—5 Months. Cold Painful Left Index Finger with Ulceration.
G
ROOM
1 2 3 4 5
RIGHT
Finger
1 2 3 4 5
LEFT
D

FIG. 14.

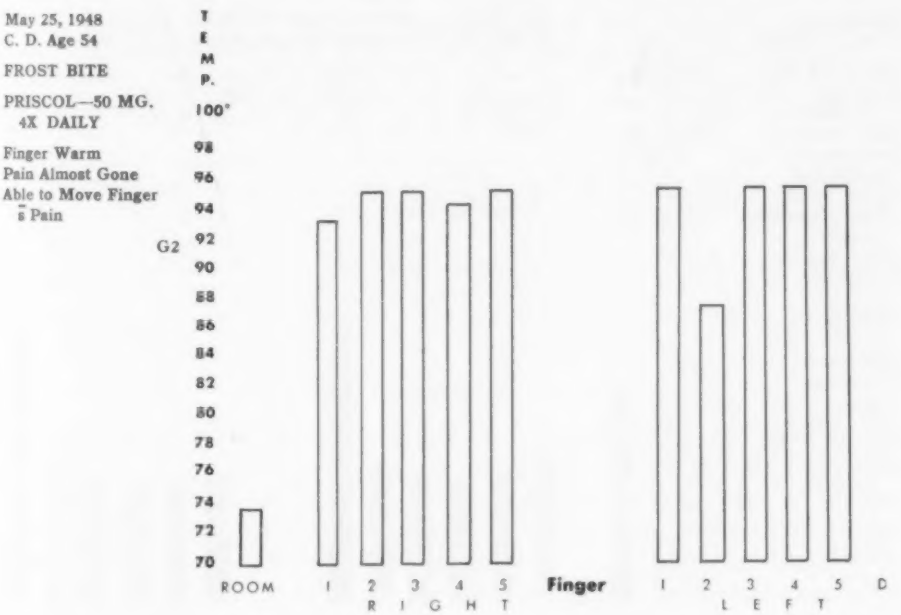
May 25, 1948
C. D. Age 54
FROST BITE
PRISCOL—50 MG. 4X DAILY
Finger Warm
Pain Almost Gone
Able to Move Finger
Less Pain
G2
TEMP.
100°
98
96
94
92
90
88
86
84
82
80
78
76
74
72
70
ROOM
1 2 3 4 5
RIGHT
Finger
1 2 3 4 5
LEFT
D

FIG. 15.

marked tenderness to palpation. The affected areas were cold to touch. The temperature of the affected fingers averaged 3.6 degrees below that of the room.

Diagnosis: Marie-Strümpell's arthritis with a radiculitis causing sympathetic irritation, with a resultant Raynaud's syndrome in the right hand.

Treatment: The patient was put on Priscoline, 25 mg. intramuscularly four times a day.

Results: The patient had a marked relief of symptoms in the right hand. The ulcerations healed. He was discharged and returned to the clinic, where he was put on oral Priscoline in a similar dosage. He has been followed by means of thermocouple readings which are gradually improving. However, the patient is still somewhat intolerant of cold.

Case 12. This 54 year old unemployed male, first seen on March 9, 1948, had had cold feet for the past four months and intermittent claudication on walking one-half block.

Physical examination revealed cold feet, rubor on dependence, pallor on elevation, minimal dorsalis pedis pulsation on right, no dorsalis pedis pulsation on left, venous filling time 26 seconds on the left, blood pressure 190 mm. Hg systolic and 90 mm. diastolic. Laboratory examinations of the blood and urine were all within normal limits. Electrocardiogram revealed right axis deviation. Roentgenogram of the legs revealed calcification of tibial arteries. Oscillometric readings were zero for both feet, one-quarter for left ankle, one-half for left calf, and one for left thigh, four for right ankle, six for right calf, and six for the right thigh. The temperature of the toes averaged five degrees below the temperature of the room.

Diagnosis: Hypertensive arteriosclerotic heart disease, anginal syndrome, occlusive arterial disease left foot.

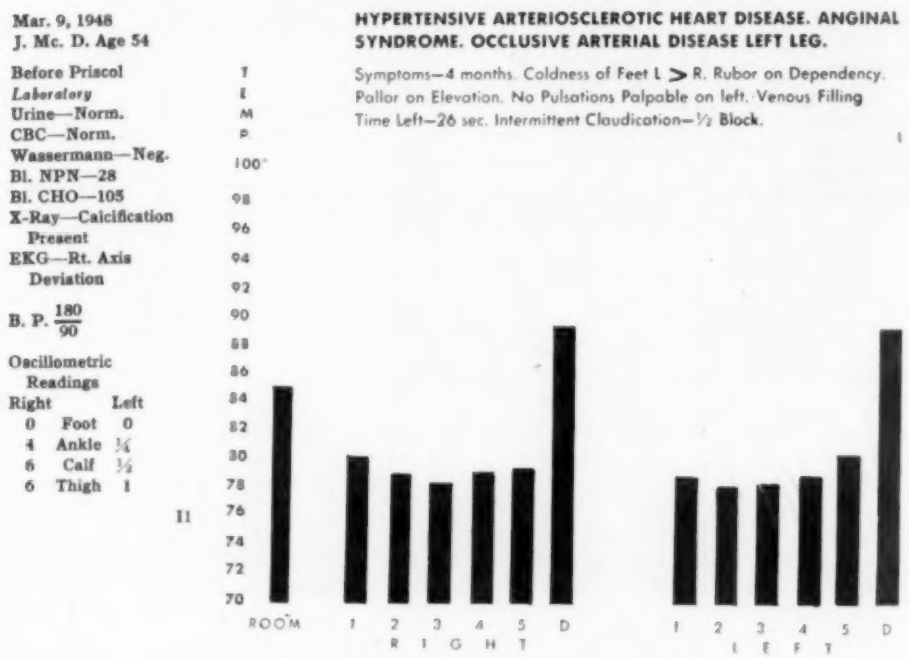

FIG. 16.

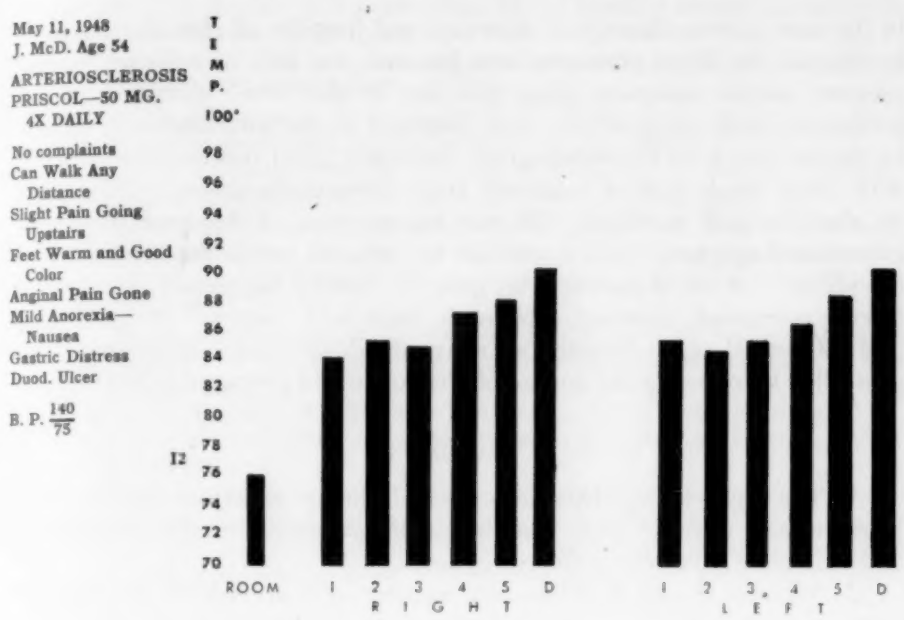

FIG. 17.

Treatment: The patient was put on Priscoline, 50 mg. orally four times a day.

Results: Two months later, the temperature of the toes averaged seven degrees above the room temperature. The patient had no complaints referable to his feet or legs. The feet were warm and of good color. He could walk any distance. The blood pressure was 140 mm. Hg systolic and 75 mm. diastolic. The anginal pain was gone. Anorexia, nausea and gastric distress were noted. Gastrointestinal series revealed duodenal ulcer. Treatment for this gave relief.

Patient is now on combined treatment and is asymptomatic. Dosage of Priscoline has been reduced to 25 mg. four times a day. Repeated laboratory examinations remain normal.

Before taking Priscoline, the patient could walk only 40 yards. On December 21, 1948 he was able to walk one mile without pain.

Figures 16 and 17 represent in graph form the studies before and after administration of Priscoline.

COMMENT

Results of treatment with Priscoline in the majority of cases studied were good. The average daily dose orally was 200 to 250 mg., taken in divided doses. The highest oral daily dose was 500 mg., taken in divided doses. The average intravenous dose was 50 mg., given three to four times a day. The greatest intravenous dose was 240 mg., given in doses of 30 mg. every four hours. All patients exhibited increased collateral circulation as demonstrated by temperature studies. Intermittent claudication was abolished or improved in most patients. All patients claimed that their feet were warmer and that they felt much better than before treatment.

In the cases of thromboangiitis obliterans and frostbite all ulcerations healed. In general, the blood pressures were lowered, but lack of sufficient studies prevents further comment along this line at this time. Contrary to expectations, fairly good results were obtained in the arteriosclerotic group. In the patients with thromboangiitis obliterans, good results were obtained with either large oral or relatively large intravenous doses. There were no alarming side reactions. Of two known cases of duodenal ulcer, one experienced epigastric pain controlled by antacids, while the other had no complaints. A third patient who gave no history suggestive of duodenal ulcer experienced anorexia, epigastric pain and nausea. A subsequent gastrointestinal series revealed an active duodenal ulcer. Symptoms were controlled by reducing the dosage of Priscoline and giving ulcer therapy.

Conclusions

1. The physiologic, pharmacologic and clinical effects of diethyl ether, histidine and ascorbic acid, vitamin E, dibenamine, tetraethyl ammonium and Priscoline have been presented in detail.

2. Vitamin E and histidine and ascorbic acid are felt to be relatively inert.

3. Diethyl ether, dibenamine and tetraethyl ammonium are shown to be fairly efficient vasodilators, but their use is often followed by severe reactions.

4. A report is submitted of the treatment with Priscoline of 22 patients at the Jersey City Medical Center.

5. Of all the drugs discussed, Priscoline and intraarterial histamine appear to be of the greatest clinical promise.

6. Finally, the treatment of peripheral vascular diseases should be based on such time-proved methods as bed rest, intermittent venous occlusion, oscillating bed, reflex vasodilatation by the distal application of heat, local and sympathetic nerve blocks, sympathectomy, vascular exercises, foot hygiene, etc. Vasodilators should be used to supplement and not to replace the above mentioned measures.

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LACK OF CORRELATION BETWEEN SYMPTOMS AND DEGREE OF RENAL IMPAIRMENT *

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In a recent publication from this laboratory [1] the work of Sirota, Baldwin and Villarreal,[2] showing that the 24-hourly volume of glomerular filtrate can be measured satisfactorily, was confirmed. In the course of our studies it became evident that the disturbances from which the patients were suffering bore no close relationship to the degree of functional impairment of the glomeruli.

It is not uncommon for the initial stages of glomerular nephritis to be wholly symptomless and its presence to be detected solely by the characteristic findings in the urine. In such instances, the patient may continue to be unaware that he is the victim of a progressive disease that is destroying the glomeruli and tubules until the damage is very extensive. Such a situation is well exemplified by the case of a 44 year old man first admitted to the University Hospital on November 12, 1948, complaining of ease of fatigue and of precordial pains. He had felt entirely well until six months prior to his admission. During this period he suffered from increasing severity of precordial pain, dyspnea on exertion, and occasional nocturnal cramps of the leg muscles. Examination revealed hypertension, cardiac enlargement and grade III bilateral retinopathy. The hemoglobin was 6.5 gm. per cent and the red cell count 2.6 M per cu. mm. Serum calcium was 8.0 mg. per cent and serum inorganic phosphorus 12 mg. per cent. Blood urea nitrogen was 152 mg. per cent, serum creatinine 17.8 mg. per cent, and the volume of the 24-hourly glomerular filtrate only 3.2 liters corrected to 1.73 sq. m. of body surface; this is 2.2 per cent of normal! The subjective disturbances in this case were attributable to myocardial degeneration combined with a severe anemia, and to hypocalcemia. The patient died 10 weeks later, and the significant postmortem findings were marked cardiac enlargement with old and recent myocardial infarcts, and thrombosis of the anterior descending branch of the left coronary artery. The kidneys were markedly contracted and coarsely granular, and on microscopic examination revealed advanced chronic glomerulonephritis. Advanced generalized atherosclerosis was also found.

Many nephritic patients are seen for the first time because they have become edematous, and they frequently volunteer the information that they had felt well prior to the appearance of the swelling and had been totally unaware that they had kidney disease. One, a 16 year old high school girl,

* Received for publication March 24, 1950.
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Aided by a grant from the United States Public Health Service.

first noticed swelling around the eyes every morning in July, 1947. Prior to this event there were no symptoms to indicate that anything was wrong with her. On December 12, 1947, she entered the University Hospital for management of a moderate generalized edema. The blood pressure was not elevated. The urine showed all the characteristic findings of glomerulonephritis. The hemoglobin was 10.9 gm. per cent and the red cell count 3.7 M per cu. mm. Total serum proteins were 4.0 gm. per cent, with serum albumin 2.7 gm. per cent. Subsequent laboratory studies have shown a progressive anemia, the hemoglobin on December 12, 1949, being 7.3 gm. per cent and the red cell count 2.8 M per cu. mm. After her admission to the hospital, edema was easily removed, and its recurrence has been prevented up to the time of writing. Throughout this period, the patient has felt well and has led the usual life of a high school student. The 24-hourly glomerular filtrate in November, 1948, was 50 liters. This has been cut down progressively to 19 liters as of December, 1949, yet the patient frequently volunteers that she "feels as well now as she ever has."

Other patients are seen for the first time after the edema has become very extensive. They complain of anorexia, nausea and distention, and some of them of serious impairment of vision and incapacitation. Nevertheless, the removal of the edema may restore the patient to a symptom-free condition even though the laboratory examinations reveal far advanced nephritis. A 19 year old Naval enlistee was hospitalized in September, 1946, when hematuria was noted. Five weeks later edema of the lower extremities appeared, and diagnosis of nephritis was made then. He was discharged from the Navy and transferred to another hospital, where massive edema developed as evidenced by a gain in weight of 80 pounds. There was progressive blurring of vision until he became unable to read even the largest type. On admission to the University Hospital in August, 1947, the fundi oculi revealed choking of the discs, angiospasms, hemorrhages and exudates. Massive generalized edema with enormous distention of the abdomen was present. The hemoglobin was 9.1 gm. per cent and the red cell count 3.1 M per cu. mm. The total serum proteins were 3.6 gm. per cent, with 1.8 gm. per cent albumin. Plasma cholesterol was 335 mg. per cent. The blood urea nitrogen was 22 mg. per cent and the hourly urea clearance 18 per cent of normal. Sharp sodium restriction and the administration of ammonium chloride resulted in a progressive lessening of edema, which eventually disappeared and was accompanied by progressive improvement in vision, which became subjectively normal. The only remaining complaint was ease of fatigue. He reported for evaluation of his condition in September, 1949. He had remained edema free and had no visual complaints. The blood pressure was 200/140 mm. Hg. No fresh hemorrhages or exudates were seen in the fundi. The hemoglobin was 9.0 gm. per cent and there were 3.3 M red blood cells per cu. mm. Total serum proteins were 4.8 gm. per cent, with 3.0 gm. per cent of albumin. The serum cal-

cium was 7.6 mg. per cent and the inorganic phosphorus 8.1 mg. per cent. The volume of the 24-hourly glomerular filtrate, corrected to body surface of 1.73 sq. m., was only 12 liters, or 8 per cent of normal.

Our studies included patients who had reached far advanced stages of renal destruction without becoming edematous at any time. A 65 year old housewife entered the University Hospital in February, 1949, with a provisional diagnosis of gall-bladder disease because of epigastric distress, anorexia, nausea and vomiting, with loss of weight of 35 pounds. In 1946, during a routine examination, a systolic blood pressure of 210 was noted, although she was entirely symptomless at the time. On admission she was semi-comatose; breathing was of the Kussmaul type; the plasma CO_2 combining power was 12 vol. per cent; blood urea nitrogen was 200 mg. per cent; the serum calcium was 4.4. mg. per cent and inorganic phosphorus was 8.6 mg. per cent; hemoglobin was 10 mg. per cent. Rapid and striking improvement occurred with partial correction of the chemical abnormalities. She was discharged on a 40 gm. protein diet, supplementary sodium in the form of sodium citrate (one teaspoonful of a 20 per cent solution twice a day) and amphojel. On this régime she has no symptoms except for occasional precordial pains, and is fully active as a farm wife even though the blood urea nitrogen is 94 mg. per cent and the serum creatinine 9.8 mg. per cent. The volume of the glomerular filtrate determined on February 3, 1950, was 7 liters (normal for her is 134 liters per 24 hours). This is only 5 per cent of normal!

Another patient, a 49 year old man admitted in coma on February 3, 1949, had noted ease of fatigue for the previous year but no other symptoms until 10 days before admission, when he became nauseated and vomited all food taken. The blood urea nitrogen then was 153 mg. per cent, the plasma CO_2 combining power 22 vol. per cent, and the hemoglobin 13.7 gm. per cent. He was in a severe state of dehydration. Following intravenous administration over a period of eight days of a 5 per cent solution of glucose, to which 200 mEq. of potassium in the form of 16 gm. of KCl had been added, he made a dramatic recovery. Since the serum potassium concentration after this treatment was only 3.2 mEq. per liter, potassium administration by mouth was continued. He became symptom-free and has remained essentially so up to the time of writing, even though the glomerular filtrate volume is only 6.6 liters per 24 hours (4.5 per cent of normal), with a blood urea nitrogen of 128 mg. per cent and a serum creatinine of 15 mg. per cent. He is presently employed as a machinist in a small factory.

Discussion

The examples cited make it clear that nephritic patients may be quite comfortable even though the volume of the glomerular filtrate is reduced to 10 per cent or less of normal. Such patients regularly show a marked increase in the nitrogenous end products of metabolism. Evidently this ac-

cumulation of nitrogenous metabolites does not result in subjective disturbances. It has been pointed out by one of us [3] that the nephritic, even in far advanced stages, rids himself of approximately all of the nitrogenous wastes of protein metabolism at their rate of production. This is accomplished by means of a simple device. Earlier work has demonstrated that the rate of increase of the blood urea nitrogen is the same as the rate of decrease of the volume of the glomerular filtrate, disregarding changes in per cent of urea reabsorbed by the tubules and changes in urea production. Accordingly, under these circumstances the product of the concentration of blood urea and the volume of the glomerular filtrate is approximately a constant. This amount of filtered urea, minus the portion of it reabsorbed by the tubules, is the amount ultimately appearing in the urine. When the reabsorption is large, blood urea nitrogen is high, and when it is small, blood urea nitrogen is low, other things being equal. For example, a patient on a constant protein diet had a 24-hourly filtrate volume of 46 liters, and the blood urea nitrogen was 14.8 mg. per cent. Accordingly, glomerular filtration resulted in 6.8 gm. of urea nitrogen (46 liters $\times$ 148 mg. per liter). Subsequently, when the glomerular filtrate had been reduced to 19 liters, the blood urea nitrogen was 34.4 mg. per cent, and this resulted in 6.5 gm. of urea nitrogen in the glomerular filtrate. In these two instances, the per cents of filtered urea reabsorbed were practically identical (56 per cent and 53 per cent). In the case of a patient who was recovering from acute nephritis, the same phenomenon is seen acting in the opposite direction. When the filtrate volume was 38 liters per 24 hours, blood urea nitrogen was 37.3 mg. per cent, resulting in the filtration of 14.1 gm. of urea nitrogen. Later, when the filtrate volume had increased to 117.4 liters per 24 hours, the blood urea nitrogen was only 11.6 mg. per cent, giving a filtration of 13.6 gm. of urea nitrogen.

The kidneys also regulate the plasma concentration of potassium, sulfate, phosphate and calcium. It is well known that marked shifts in levels of serum potassium are accompanied by important subjective disturbances. Anyone who takes the usual amounts of food necessarily absorbs roughly 70 mEq. of potassium (2.7 gm.) daily. The normal individual, with 150 liters of glomerular filtrate and a normal serum potassium concentration of 5 mEq. per liter, delivers to the tubules 750 mEq. of potassium (29 gm.), but since this individual is in potassium balance, the urine would contain only 70 mEq. of potassium, and therefore 680 mEq. of potassium must necessarily have been reabsorbed by the tubules. In the case of severe nephritis, when the glomerular filtrate volume may be 5 liters per 24 hours and the patient is eating normally, the situation is strikingly different. It was shown by Leaf and Camara [4] that such patients are usually still able to maintain normal serum concentration of potassium. Consequently, a filtration of only 25 mEq. with a urinary excretion of the same order as the amount ingested can only mean active secretion of potassium by the tubules. In the case of patients eating small amounts of food or none at all, a negative

potassium balance may develop, since noteworthy amounts of potassium continue to be lost in the urine. It would appear to be true in such cases that diminishing volumes of glomerular filtrate are actually beneficial to the patient, in the sense that less potassium is lost by filtration.

Sulfate and phosphate are end-products of metabolism. The metabolism of 200 gm. of beef (raw weight) yields 36 mEq. of $HPO_4^=$ and 25 mEq. of $SO_4^=$. Since these two anions are normally present in the plasma to the extent of only 1 to 2 mEq. per liter, practically all of the metabolic yield of them is excreted in the urine. Because the glomerular filtrate contains 1 to 2 mEq. per liter of these substances, this requires a filtrate volume of at least 25 liters per 24 hours for a low protein diet, assuming that no portion of them is removed by active tubular secretion. These conditions account for the marked elevations of these two substances in the plasma of severely nephritic individuals. The increase of these two anions replaces bicarbonate equivalently, and accounts for the very common finding of low CO_2 combining power in such patients. Since this phenomenon develops quite slowly, the necessity for excreting large amounts of CO_2 rapidly does not occur. Accordingly, there will be only a minute increase in the volume of respiration in any short interval of time. This minor change in respiration is far too small to be detected subjectively.*

It is true, however, that increases in plasma phosphate are accompanied by decreases in plasma calcium, and when the latter is seriously depleted the patients may suffer from muscle cramps. In this roundabout manner the diminished filtrate volume can be held accountable for the muscle cramps.

The occurrence of edema, so commonly seen in glomerulonephritis, is attributed to loss of serum albumin and is totally unrelated to the changing volume of the glomerular filtrate.

This leaves the anemia and the hypertension, which are such common accompaniments of nephritis, to be considered. It is true that anemia commonly accompanies glomerulonephritis. However, there is little correlation between the severity of anemia and the degree of impairment of glomerular function. We have seen some patients in the early stages of the disease with grave anemia. On the other hand, we have followed a number of patients whose filtrate volume has fallen to less than 10 per cent of normal but who do not show serious diminution of hemoglobin or red blood cells. It should be added that some of our patients incapacitated with grave anemia can be temporarily brought back to a symptom-free state by sufficient transfusions of blood. At this juncture we would like to mention the case of a 32 year old woman who was seen originally in an edematous state in 1944. Her blood pressure then was 180/114 mm. Hg, and the hemoglobin 9 gm. per cent. She was re-admitted a number of times because of weakness and shortness of breath on exertion, with morning nausea

*This is quite different from the situation in diabetic ketosis, where there is a continuing large production of ketone bodies which accordingly necessitate the rapid expulsion of large volumes of CO_2. This accounts for the marked hyperpnea observed in such cases.

and vomiting. These symptoms were temporarily relieved by transfusions of blood. Subsequently, following a period of menorrhagia, her hemoglobin diminished to 5.5 gm. per cent with a red cell count of 1.7 M per cu. mm., and she became completely incapacitated because of extreme weakness and dyspnea. The hemoglobin was brought up to 12 gm. per cent by repeated transfusions of washed red cells, whereupon she insisted that she felt entirely well. The glomerular filtrate volume then was 8 liters per 24 hours, which is 7 per cent of normal for her body size. This case again indicates that the symptomatology of such patients is not directly related to the diminished volume of the glomerular filtrate.

Hypertension in glomerulonephritis comes late and advances with progression of the disease. There is then a broad parallelism between progressive elevation of the blood pressure and diminishing renal function. On the other hand, the hypertension per se may be symptomless. So it can be stated that there is no close relationship between lessening renal function and subjective disturbances referable to hypertension.

Even though the symptomatology of glomerulonephritis cannot be related to the extent of functional impairment of the kidneys, we have no intention of implying that the measurement of the glomerular filtrate does not yield valuable information. It is certainly true that such measurements give quantitative information about the extent of renal impairment at the time, and about the rate at which the disease is advancing.

Conclusions

The continued study of a group of patients suffering from glomerulonephritis has brought to light the fact that it is impossible to correlate symptoms and degree of functional impairment of glomeruli. Patients whose volume of glomerular filtrate has been reduced to 10 per cent of normal or less may be symptom-free.

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BACTERIAL ENDOCARDITIS: CLINICO-PATHOLOGIC STUDIES OF UNTREATED, TREATED AND CURED PATIENTS *

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THE development of effective treatment for bacterial endocarditis [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16] has altered certain clinical and pathologic features of the disease which have received only cursory study. Pathologic data such as the mode of disability and death assumed great significance with the advent of effective therapy, not only in relation to cure but to the future health and longevity of the patient.

To correlate the changes in clinical and pathologic findings of untreated and treated cases, to study the effects of the disease and its healing on the health and longevity of surviving patients, and to reëxamine the incidence and types of inciting disease, we have studied the clinical course and, where available, the postmortem tissues of 70 patients diagnosed by clinical findings and blood culture as bacterial endocarditis. Twenty-three were symptomatically treated, 11 were treated with sulfonamides and 36 with antibiotics. Initial attempts to discard patients with obvious acute bacterial endocarditis proved ineffective because of our inability to differentiate the treated patients. Hence we included all treated cases of proved bacterial endocarditis in this analysis.

CLINICAL DATA

Preëxisting Infections: A satisfactory history of the presence or absence of predisposing disease was found in 60 cases. Thirty (50 per cent) of these had a recognizable predisposing illness: sore throat in 20 (33.3 per cent), dental extractions in five (8.3 per cent), spontaneous delivery in three (5 per cent) and pelvic surgery in two (3.3 per cent). The importance of rigorous prophylactic treatment in the presence of predisposing factors has been frequently emphasized since the availability of effective therapy. Unfortunately the ideal therapeutic agent, effective dose and duration of therapy are still unsettled problems awaiting solution through clinical experience.

Causes of Death in Untreated, Sulfonamide-Treated and Antibiotic-Treated Patients: It has been stated, from information gained before the days of adequate treatment, that heart failure is an unimportant factor in

* Received for publication July 14, 1950.

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Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

death from bacterial endocarditis.[17, 18] To evaluate its importance and to determine its increased significance with effective therapy, we reviewed the major causes of death in all our patients. These are shown in table 1. Heart failure was the immediate cause of death in 39.1 per cent of untreated patients who died, 93.8 per cent of antibiotic-treated patients and 100 per cent of sulfonamide-treated patients. Embolic cerebral phenomena, which were responsible for 39.1 per cent of the deaths in the untreated group, caused no deaths in either of the treated groups. The percentage differences in the development of heart failure were found to be of high statistical significance when evaluated by a test of the differences between two percentages.*

The advent of effective treatment brought a shift in the cause of immediate death, and heart failure emerged as the single important factor in the immediate mortality. To determine whether this was due to increased valvular deformity,[4, 13, 19, 20, 21, 22] myocarditis, or a combination of factors,[23, 24, 25, 26, 27, 28, 29, 30] we studied their relative importance by examining their

TABLE I

Major Cause of Death in Untreated, Sulfonamide-Treated and Penicillin-Treated Patients

	Untreated	Sulfonamide-Treated	Penicillin-Treated
No. patients	23	11	36 patients with 42 infections
Immediate mortality*	23 (100%)	11 (100%)	16 (44.4%)
Heart failure	9 (39.1%)	11 (100%)	15 (93.8%)
Cerebral accidents	9 (39.1%)	0	0
Pulmonary infarcts	2	0	0
Other	3	0	1

* The immediate mortality includes all patients dying within three months of termination of therapy.

frequency and extent in autopsy studies of the untreated and treated cases. The findings are discussed later.

The type of pathogenic organism found on blood culture, underlying heart disease, symptoms and physical findings were not unusual and will not be presented in detail here. We were interested in the relation of the duration of symptoms, age of the patient, valves involved and the presence or absence of heart failure to the cure of the individual, his health and his life span. Also of interest was the incidence of reinfections and possible reasons therefor in cured patients. To study the relationships of these factors, we used the group of 36 antibiotic-treated patients, representing 42 infections or reinfections.

Clinical Cure in Antibiotic Treated Patients: Clinical cure as indicated by negative blood cultures and abatement of all clinical evidences of infection three months following the discontinuance of therapy was attained in 25 patient-infections, a percentage cure of 60.

* The statistical analysis and testing of this and the following tables were done by J. V. Talacko, D.Sc., Dept. of Mathematics, Marquette University.

The incidence of treatment failures was high because several patients were treated late with inadequate dosage for insufficient periods of time.

In the 25 patient-infections resulting in cure there were reinfections in six (29 per cent). These reinfections resulted in immediate death from heart failure in one patient, and death occurred from progressive heart failure two years after clinical cure of the reinfection in a second instance. In a third instance the patient left before completion of retreatment and his

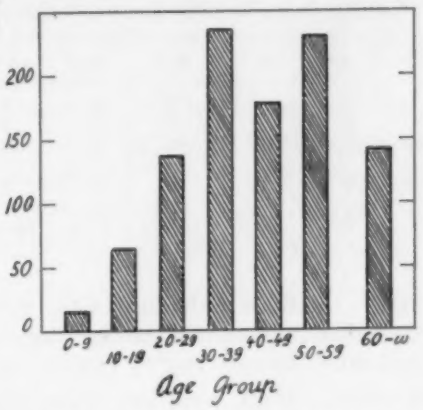

FIG. 1. Ratio-incidence of bacterial endocarditis. Distribution of 1,000 patients of bacterial endocarditis from an ideal population with equal age groups.

subsequent course is unknown. The remaining three were cured without further recognized damage. In all six reinfections there was a history of infection or an operative procedure antedating the recurrence of the bacterial endocarditis.

Age Incidence: The age incidence of the disease is shown in table 2 and suggests that the incidence from ages 30 to 60 is relatively constant. This is more strikingly shown in figure 1, where the predicted incidence of 1,000

TABLE II

Incidence of Bacterial Endocarditis by Decades in 70 Patients

Age	0–9	10–19	20–29	30–39	40–49	50–59	60+
Cases	1	5	12	19	13	13	7

cases of bacterial endocarditis by age groups in Milwaukee is illustrated. This incidence was computed from the figures in table 2 and the distribution of the population of Milwaukee by decades as determined in the 1940 census. From ages 30 to 60 the incidence is relatively constant, and the apparent frequency of the disease from 30 to 39 is principally an expression of the larger population in that age group. The low incidence from ages one to 19 is due in part to the fact that our patients were from a veterans' hospital

and a county general hospital in a city where a large children's hospital receiving municipal support assumes the care of a portion of the children of indigent families.

Significance of Patients' Age at Time of Infection: The age of the patient at the time of infection has been stated to be a significant prognostic factor

TABLE III

Relation of Patient's Age to Immediate and Eventual Cardiac Mortality and Increased Cardiac Disability in 36 Penicillin-Treated Patients

Age of Patient	0–9	10–19	20–29	30–39	40–49	50–59	60+
No. patients	1	3	7	12	3	4	6
Immediate cardiac deaths	0	1	1	4	1	3	5
No. living with increased cardiac disability	0	0	0	3	0	0	1
No. dying of heart failure within two years	0	0	0	2	1	1	0
% death or increased disability	0%	33.3%	14.3%	75%	66.6%	100%	100%

in the immediate mortality.[13] In table 3 the age of the patient is related to the immediate cardiac mortality, subsequent cardiac mortality and cardiac disability in surviving patients. Among the 11 patients under 30 years of age (representing 12 infections), there were two immediate cardiac deaths and no subsequent demonstrable impairment of cardiac function or subsequent cardiac mortality. Of the two immediate cardiac deaths (deaths

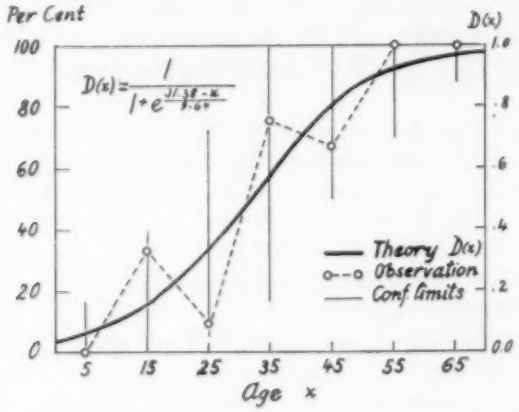

FIG. 2. The probability curve of the percentage of cardiac mortality and morbidity two years after successful penicillin therapy in the various age groups.

during treatment or within three months of its discontinuance), one died of progressive heart failure subsequent to erosion of an aortic cusp. The other represented a long-standing infection in a patient who had heart failure before treatment was started and in whom there was clinical lessening of the infection but progression of the heart failure.

The total mortality and increased morbidity percentage in the 12 infections before the age of 29 is 16.6; between the ages of 30 and 39 it is 75; between 40 and 49 it is 66.6 per cent, and 100 thereafter.

These figures are of high statistical significance when subjected to the Chi-square test, and they support the contention that the age of the patient is important in prognosticating the immediate mortality, increased cardiac impairment, and subsequent cardiac mortality of treated and bacterially cured patients. In figure 2 the predicated percentage of cardiac mortality and increased morbidity two years after successful penicillin therapy is shown for patients of various ages.

Significance of Duration of Infection before Treatment: The relationship between the duration of symptoms and the immediate mortality in treated patients has been disputed.[13, 22, 29] In table 4 there are related the duration of symptoms before treatment to the immediate cardiac mortality, subsequent increased cardiac disability and subsequent cardiac mortality of survivors

TABLE IV

Relation of Duration of Symptoms Untreated to Immediate and Subsequent Mortality and Subsequent Increased Cardiac Disability in 34 Penicillin-Treated Patients

Weeks before Treatment	0–10	11–20	21+
No. patients	17	12	5
Immediate cardiac mortality	5	4	4
No. living with increased cardiac disability	2	2	0
No. dying of heart failure within two years	2	2	0
% death or disability	53%	66.6%	80%

in the 34 patients with this information available. When treatment is instituted within 10 weeks of the onset of symptoms, the incidence of death or increased cardiac disability is 53 per cent; when instituted within 11 to 20 weeks, 66.6 per cent; when instituted after 21 weeks, 80 per cent.

The test of statistical independence shows these figures to be of no significance because of the small number of patients involved. Final decision as to whether the duration of symptoms without treatment will increase the cardiac mortality and morbidity must await analysis of larger groups of patients.

Significance of Heart Failure during Treatment: The occurrence of heart failure developing during and as a result of the infection has been considered a serious prognostic sign.[13, 29] Our findings relating the presence of heart failure before treatment to the immediate and subsequent cardiac mortality and increased cardiac morbidity of survivors are shown in table 5. The incidence of death or subsequent cardiac disability is 100 per cent for those in heart failure during the period of treatment as against 35 per cent

for those without heart failure during this period. The Chi-square test shows a high degree of statistical significance in these figures.

Of the 36 patients representing 42 infections, 16 were in heart failure before or during active treatment. This represents 38.1 per cent of the patient-infections and is approximately the percentage of patients without treatment dying of heart failure. It suggests that our reduced mortality

TABLE V

Relation of Heart Failure during Treatment to the Immediate and Subsequent Cardiac Mortality and Subsequent Increased Cardiac Disability in 36 Penicillin-Treated Patients

	Heart Failure During Rx.	No Heart Failure During Rx.
No. patients	16	20
Immediate cardiac mortality	14	1
No. living with increased cardiac disability	0	4
No. dying of heart failure within two years	2	2
% death or disability	100%	35%

through treatment depends largely upon the prevention of fatal embolic complications.

The occurrence of heart failure during treatment is a most serious prognostic sign. In our series, 87.5 per cent died during treatment or within three months thereafter, and the remaining 12.5 per cent died of heart failure within two years.

Significance of the Valve Involved: Many references in the more recent literature stress the importance of progressive aortic valvular involvement

TABLE VI

Relation of Valvular Lesions to Immediate and Subsequent Cardiac Mortality and Increase in Cardiac Disability in 33 Treated Patients. (Congenital lesions other than valvular are excluded.)

Valves Involved	Mitral Valve	Aortic Valve	Aortic and Mitral Valve
No. patients	14	8	11
Immediate cardiac mortality	7	4	4
No. living with increased cardiac disability	1	1	1
Subsequent cardiac death	0	1	3
Per cent cardiac mortality or disability	57.1%	75%	72.7%

in the cardiac mortality and subsequent cardiac disability.[4, 13, 19, 20, 21, 22, 29] The relation of the involved valve to the immediate cardiac mortality, later cardiac mortality and increased cardiac impairment in survivors is shown in table 6. In those patients still living with bivalvular disease it was impossible to determine if one or more valves were involved by the infection.

In the postmortem series, only the valve or valves involved by vegetations were used in designating their classification.

There is an apparently higher morbidity and mortality in aortic and combined valvular lesions than in mitral valvular lesions alone, although statistical analysis shows the differences to be without significance (Chi-square test) in the number of patients studied.

It is interesting that two patients developed the classical evidences of dynamic aortic insufficiency which led to the rapid development of heart failure and death with clinical impression of ruptured aortic cusps. On postmortem examination both patients had mitral valvular involvement alone, one with perforation of the anterior cusp of the mitral valve, and both with extremely dilated left ventricles and functional incompetence of the aortic valve. Two other patients were encountered whose postmortem examinations disclosed perforation of the mitral cusp and rupture of the chordae tendineae, respectively, leading to heart failure with evidences of aortic insufficiency. One had healed rheumatic aortic insufficiency, the other had no aortic involvement. Whether the aortic insufficiency was evidenced before infection or increased during observation was not recorded. These cases emphasize the difficulties encountered in the clinical classification of the valve involved by the infection and the possible error in ascribing increasing signs of aortic insufficiency to increasing aortic valvular damage. In a small series of cases such as are here reported, a considerable statistical error can occur. This may in part explain the difference between our figures and others that have been reported.

Cardiac Disability in the Cured Patient: In the bacterially healed patients in our series there was evidence of moderate to marked impairment in cardiac function in eight of the 21 surviving patients, representing 25 infections or reinfections (32 per cent). Four of these patients subsequently died of progressive heart failure (16 per cent).

Thus, although 60 per cent of the patients receiving effective antibiotic therapy survived the infection, 32 per cent of the survivors had serious impairment of cardiac function, which progressed to death from heart failure within two years in 16 per cent.

Pathologic Data

The mechanism of death in bacterial endocarditis received but scant attention in the pathologic studies prior to the advent of antibiotic therapy.[23, 24, 25] Earlier authors believed that heart failure was an insignificant factor in the mortality of bacterial endocarditis.[17, 18] Others thought that heart failure, often associated with myocarditis,[23, 24, 25] was important as a contributory or major factor. The pathologic changes in the affected valves were studied, but only occasionally was mention made of the healing tendency present in most cases. This tendency to heal becomes significant, if therapy is effective by virtue of augmenting this process.

In our study we used the pathologic tissues of 48 patients, 22 untreated, eight treated with sulfonamides, and 18 with penicillin. Pathologic changes were evaluated without reference to the clinical findings as to the cause of death, extent of myocarditis, valvular involvement and healing. The active myocardial changes were diffuse, focal, or a combination of the two. The diffuse myocarditis (figure 3) was characterized by leukocytes within the interstitial tissues, edema and, later, diffuse fibrosis as healing progressed.

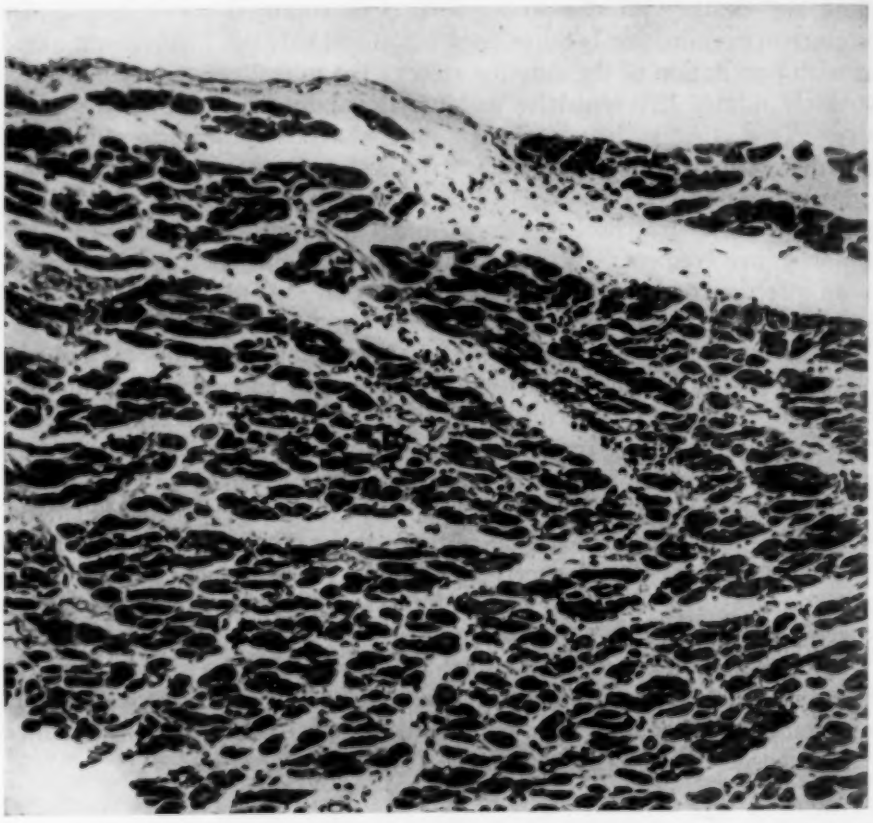

FIG. 3. Diffuse myocarditis: Lymphocytes and monocytes within edematous interstices.

The focal type (figure 4), occasionally with demonstrable embolic origin, has been called the "Bracht-Wächter body." This was seen in the acute, subacute and healed forms. As might be expected, many of the patients, especially in the older age groups, exhibited diffuse fibrotic changes associated with arteriosclerosis.

Pathologic Cause of Death in Untreated and Treated Patients: The importance of heart failure as the main cause of death in untreated, sulfonamide-treated and antibiotic-treated patients subjected to postmortem examination

is shown in table 7. The similarity to the clinical series is readily seen by comparison with table 1.

Relationship of Heart Failure to Presence of Myocarditis: This relationship is indicated in table 7. Heart failure was present in 14 (63.6 per cent)

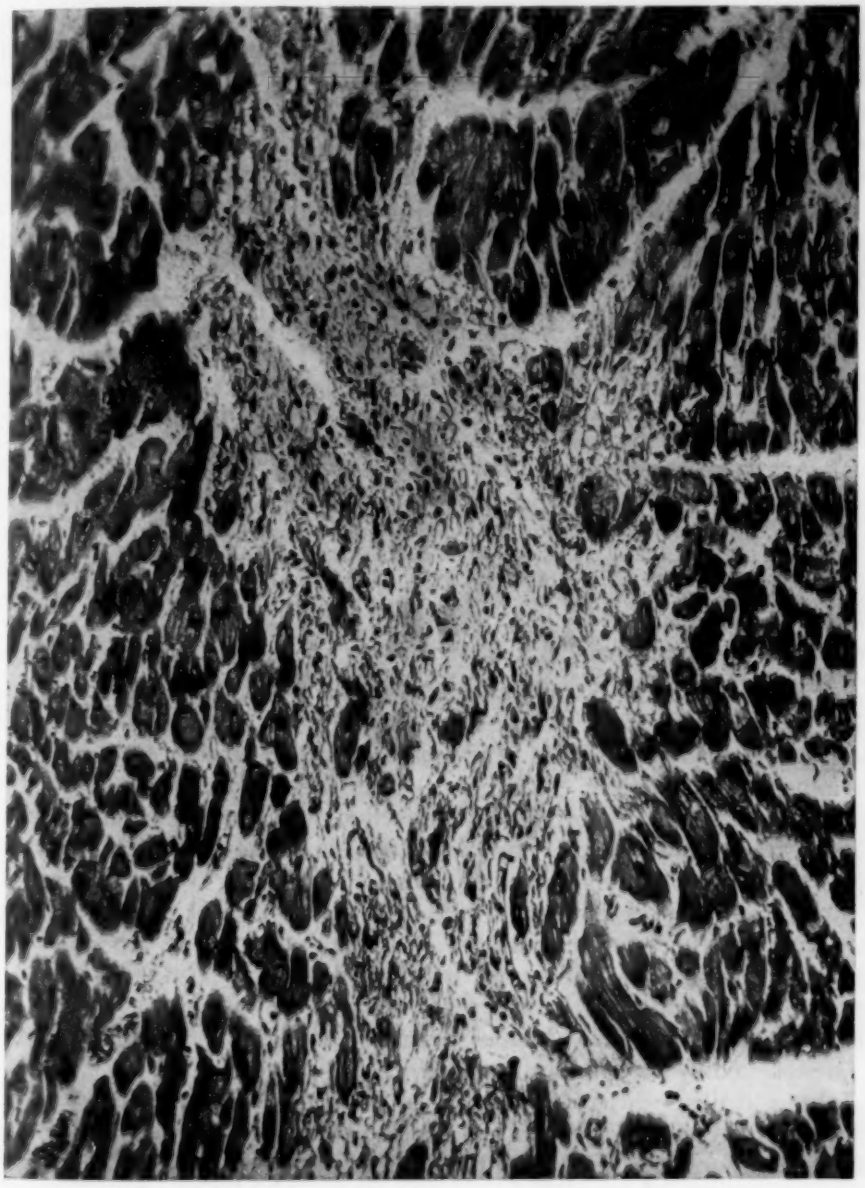

FIG. 4. Focal myocarditis: "Bracht-Wächter body." Granulation tissue replacing myocardium.

of the 22 untreated patients studied pathologically. The routine number of myocardial sections showed moderate to marked evidence of acute or subacute myocarditis in 11 (80 per cent) of those in heart failure. Two of the three patients dying in heart failure without significant myocarditis were in heart failure several years before developing bacterial endocarditis. The third died of pulmonary infarction, with heart failure associated with marked diffuse myocardial fibrosis and mild acute myocarditis. The duration of infection was not determined in any of the three. In the eight patients dying without clinical or pathologic evidence of heart failure, myocarditis was present in three (37.5 per cent) and absent in five (62.5 per cent). In these three cases, however, the duration of symptoms was not more than eight weeks before death occurred from noncardiac causes. This suggests that death from embolism occurred before heart failure could develop.

The eight sulfonamide-treated patients all died with heart failure, and moderate to marked acute or subacute myocarditis was present in all.

TABLE VII

The Presence of Heart Failure Related to Myocarditis in 48 Cases of Bacterial Endocarditis Examined Post Mortem

	Total Cases	Heart Failure Present	Heart Failure Chief Cause of Death	Active Myocarditis Without Heart Failure	Active Myocarditis With Heart Failure
Untreated cases	22	14	8	3	11
Sulfonamide-treated cases	8	8	7	0	8
Penicillin-treated cases	18	18	17	0	13

The 18 antibiotic-treated patients who died all had heart failure and all showed evidence of active or healed myocarditis. Fourteen patients had active infections (i.e., died during treatment or within three months of its termination). Thirteen (92.8 per cent) of these had moderate to marked active myocarditis. One was a reinfection after one year of cure and demonstrated marked acute myocarditis. Three showed marked subacute myocarditis with minimal scarring. Two inadequately treated patients had acute myocarditis of marked degree, and seven showed marked subacute myocarditis. One patient with death from heart failure in the twelfth week of the infection presented minimal acute myocarditis and marked diffuse myocardial fibrosis with perforation of the interventricular septum. The affected valves showed no evidence of healing. The heart failure was not explained by the myocarditis present.

Four patients died of heart failure eight months to three years after clinical arrest of the infection and showed no active myocarditis, but they did exhibit moderate to marked diffuse microscopic scarring which we considered probable healed lesions of myocarditis. In all four the aortic valve was involved, and in three there was involvement of the mitral valve also.

In three of the four, aortic valvular incompetency was marked, as was the postmortem evidence of aortic valvular deformity.

From these figures, all of which are statistically significant as evaluated by the Chi-square test, it can be seen that a moderate to marked myocarditis occurred in 32 of the 36 patients (90.0 per cent) who died in heart failure during the period of active infection. In the eight patients dying without heart failure during the active infection, myocarditis was present in three (37.5 per cent), and all of these three died of embolic complications before the eighth week of the infection. The conclusion appears inescapable that the association of myocarditis with heart failure is important during the active phase of the disease. In the heart failure which develops later in the cured cases, valvular deformity, especially aortic, is a more significant factor.

Relation of Healing of Vegetations to Treatment: A point of practical importance to remember is that partial healing of varying degree of the involved valve or valves occurs in many untreated cases of bacterial endocarditis. This may explain the healing observed in certain cases treated

TABLE VIII

Valvular Healing Related to the Type of Treatment in 35 Postmortem Cases of Bacterial Endocarditis

	Total	No Healing	1+ Healing	2+ Healing	3+ Healing	Healed
Untreated cases	14	0	12	2	0	0
Sulfonamide-treated cases	3	0	2	0	1	0
Penicillin-treated cases	18	1	0	5	6	6

with theoretically suboptimal doses as determined by in vitro sensitivity of the organism to sulfonamides and antibiotics.

Table 8 shows the extent of healing observed in the valves in 14 untreated, three sulfonamide-treated and 18 antibiotic treated cases of bacterial endocarditis. The unhealed vegetations are characterized by a network of fibrin on the surface, with imbedded red cells, polymorphonuclear cells and bacteria. Beneath are varying degrees of organization on the base of the collagenous valve. With healing there is endothelialization progressing centrally until complete, with increasing granulation, calcification and fibrosis replacing the fibrin mass. The healed vegetation is eventually completely endothelialized, with fibrous tissue and often calcification beneath. Grossly and microscopically it may be difficult to differentiate from a healed rheumatic verruca.

In the 14 untreated cases with valve sections available for study, there was evidence of healing in all, the minimal evidence being slight to moderate organization at the base of the vegetation in 12 (85.7 per cent), and moderate healing characterized by moderate endothelialization and organization in two (14.3 per cent). Of the three sulfonamide-treated patients, two

showed slight healing and one marked healing. Of the 18 antibiotic-treated patients, healing was complete (endothelialization and organization) in six (33.3 per cent), marked but not complete in six (33.3 per cent), moderate in five (27.7 per cent) and without evidence of healing in one (5.5 per cent). All deaths from embolic phenomena uncomplicated by heart failure occurred in the patients whose vegetations showed minimal healing. This also suggests that a major effect of treatment in reducing the mortality is to reduce embolism through healing of the vegetation.

Conclusions

The change in the immediate mortality of bacterial endocarditis from nearly 100 per cent to approximately 35 per cent, brought about by effective antibiotic therapy, was due to two factors. These were early healing of the vegetations, with resultant decrease in the fatal embolic complications, and the institution of treatment before the development of myocarditis associated with heart failure. Halting the surface growth of the bacterial colonies allowed time for the host to organize the vegetation adequately, thus inhibiting embolism which caused 47 per cent of the deaths in untreated patients. Occasionally heart failure developed as a result of excessive valvular destruction, but usually it resulted in association with the development of myocarditis because of delay in diagnosis and treatment. If the patient had symptoms for several months, myocarditis was almost invariably present in association with heart failure, which was usually fatal. For these reasons a delay in treatment seriously affected the prognosis for immediate cure.

The age of the individual at the time of the infection was important. The mortality steadily increased beyond the age of 30. Incidentally, in our series correction for the distribution of population by decades revealed the incidence of the disease from 30 to 60 to be remarkably constant.

When heart failure developed during the active phase of the disease, the immediate mortality was markedly increased (87.5 per cent). Subsequent cardiac disability of marked degree was practically assured, and death within two years from heart failure was likely under these circumstances.

The late morbidity and mortality in adequately treated patients were caused almost entirely by heart failure. Increasing valvular deformity, particularly of the aortic valve, was of prime importance, whereas myocardial fibrosis due to the residuals of myocarditis was of undetermined but lesser significance.

Increased cardiac disability developed in approximately one-third of those cured of the infection. In approximately one-fifth, death from heart failure occurred within two years.

To improve these morbidity and mortality figures it will be necessary (1) to prevent the bacterial infection by recognition and treatment of the common predisposing factors, and (2) to recognize and treat the disease before fatal embolism or heart failure occurs. Strict attention to prophy-

laxis is especially important in all cardiac patients beyond the age of 30 because of the significantly increased cardiac morbidity and mortality in the later age periods.

Recognition of the fact that 30 per cent of patients who recover from the infection will have increased cardiac difficulty, and that all infections of any duration will have extensive myocarditis, is a warning that gradual and carefully supervised rehabilitation is indicated and may be helpful in limiting the cardiac crippling.

SUMMARY

1. A clinicopathologic and statistical analysis of 23 untreated, 11 sulfonamide-treated and 36 penicillin-treated patients with bacterial endocarditis was presented. Postmortem tissues were studied in 48 of the cases.

2. The causes of death in untreated and treated cases and the incidence and reasons for increased morbidity and late mortality in the treated cases were discussed.

3. The association of myocarditis with heart failure during the active phase of the disease and of increased valvular deformity with heart failure in the bacterially cured patients was emphasized.

The authors are indebted to the following pathologists for making their material available for this study:

Dr. Joseph Kuzma, Milwaukee County General Hospital, Wauwatosa, Wisconsin.
Dr. W. A. D. Anderson, St. Joseph's Hospital, Milwaukee, Wisconsin.
Dr. L. J. VanHecke, St. Luke's Hospital, Milwaukee, Wisconsin.

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LEUKEMIA AND PREGNANCY: REPORT OF FOUR CASES AND REVIEW OF THE LITERATURE*

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Three cases of leukemia associated with pregnancy have been studied in this department since 1941, and a fourth case has been obtained from the files of the Kansas City General Hospital. These four cases are herewith reported.

Case Reports

Case 1. A 25 year old woman, six and one-half months pregnant, was admitted to the Kansas City General Hospital on July 12, 1937, complaining of vaginal bleeding during the preceding week. She had had two full-term normal deliveries, and two abortions, which were performed seven years and three and one-half years previously. Examination showed a soft blowing systolic pulmonic murmur, a normally enlarged uterus, normal fetal heart tones and movements, and a slight amount of bleeding from the cervix. Her blood picture was as follows: sedimentation rate 25 mm.; serologic test for syphilis negative; 68 per cent hemoglobin, 3.53 million red blood cells, 31,150 white blood cells with 70 per cent filamented neutrophils, 14 per cent nonfilamented neutrophils, 15 per cent lymphocytes, and 1 per cent eosinophils. She was observed for four days, had no more bleeding, and was sent home.

She was readmitted on August 28, about six weeks later, again complaining of vaginal bleeding. A placenta previa was considered but was not confirmed by roentgen-ray. The only blood work done was the following: 71 per cent hemoglobin and 11,200 white blood cells. She was sent home 15 days later.

She was admitted for the third time on October 4, 1937, at term and in labor. The blood picture then was as follows: 71 per cent hemoglobin, 34,300 white blood cells, 61 per cent filamented neutrophils, 22 cent nonfilamented neutrophils, 12 per cent lymphocytes, 3 per cent basophils, 1 per cent monocytes and 1 per cent metamyelocytes. The blood serology was negative. The labor, delivery and puerperium were not remarkable, and she was sent home on the eleventh post-partum day. The baby was apparently normal.

She was admitted for the fourth time on August 23, 1938, about 10 months after delivery, complaining of a lump in her left side. Further questioning revealed that her local doctor had removed a "tumor" from her left arm three years previously and had stated her spleen was enlarged at that time. The patient herself had been able to palpate the lump in her left side for the past two months. Her blood picture at this time was as follows: 37 per cent hemoglobin, 3.39 million red blood cells, 125,000 white blood cells, 39 per cent filamented neutrophils, 22 per cent nonfilamented neutrophils, 9 per cent lymphocytes, 2 per cent myeloblasts, 18 per cent myelocytes, 9 per cent metamyelocytes and 1 per cent basophils. Her spleen was palpable. The diagnosis of chronic myelogenous leukemia was made and roentgen-ray treatment was started. She was sent home on August 30, 1938, only to return two weeks later with mucous membrane bleeding and cutaneous ecchymoses. At this time her blood serology was reported as positive; it was negative, however, on all subsequent tests.

On March 25, 1939, she was admitted for the sixth time, with vaginal bleeding. This followed a therapeutic abortion done at another hospital several days before.

*Received for publication February 22, 1950.
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Her physician felt that leukemia was an indication for terminating the pregnancy, which was done at about two and one-half months. Her post-abortion bleeding was readily controlled and her blood picture at this time was 25,000 white blood cells with 75 per cent filamented neutrophils, 14 per cent nonfilamented neutrophils, 7 per cent lymphocytes, 1 per cent metamyelocytes, 2 per cent myelocytes and 1 per cent basophils. She was sent home after five days' hospitalization.

Six months later she was again seen, this time with an abscessed tooth. Her white count was 45,000, with 10 per cent metamyelocytes and 15 per cent myelocytes. She was dismissed on October 3, 1939, but was again admitted four days later with the same complaint.

The ninth admission was September 18, 1940, because of extreme faintness, weakness and a pregnancy of two months' duration. Her white count was 11,400 with 72 per cent neutrophils. The hemoglobin was 40 per cent. A therapeutic abortion was done on October 10, followed by slight intermittent bleeding for eight days. After this time she started serious uterine bleeding which required 20 blood transfusions and two curettages before it was finally stopped five weeks later. She was dismissed on December 4, 1940.

During the next two months she was admitted three times, the final admission being on February 22, 1941. Her hemoglobin was 34 per cent and the white count 51,500. The course was progressively downward and she died on March 13, 1941.

Autopsy revealed the classic findings of chronic myelogenous leukemia. The spleen weighed 2,900 gm. and the liver 4,650 gm.

Case 2. A 25 year old woman was admitted to St. Luke's Hospital on January 7, 1941, at term and in labor. Her prenatal course, history of past illnesses and family history were not remarkable except for a "miscarriage" at six weeks on December 2, 1939, the cause of which is unknown. The labor lasted four hours, and the delivery and puerperium were complicated only by a slight excess vaginal bleeding for about one hour post-partum. A routine blood count on admission, however, showed the following: 64 per cent hemoglobin, 2.843 million red blood cells, 96,900 white blood cells, 67 per cent neutrophils, 28 per cent myelocytes and 5 per cent lymphocytes. The platelet count was 819,360 and the blood chemistry, including the non-protein-nitrogen, creatinine, sodium chloride and glucose, were within normal limits. The basal metabolic rate was plus 3.

The infant weighed 6 pounds 12 ounces and showed no evidence of leukemia. The mother and infant were dismissed on the twelfth post-partum day. On February 5, about one month after delivery, the patient was re-admitted with a breast abscess, which was drained. Her blood picture on admission was as follows: 64 per cent hemoglobin, 3.35 million red blood cells, 96,000 white blood cells, 28 per cent mature neutrophils, 34 per cent stabs, 23 per cent juveniles, 7 per cent myelocytes, 5 per cent myeloblasts, 2 per cent lymphocytes and 1 per cent eosinophils. She was dismissed on the eighth hospital day feeling much improved, but with a white blood count which had increased to 234,750.

The third admission was on October 23, 1941, because of vaginal bleeding of four months' duration. The spleen at this time filled half of her abdomen, and she had palpable right axillary glands. The histologic examination of tissue obtained on uterine curettage showed a secretory endometrium infiltrated with myeloid cells. Her white blood cell count was 344,500, with 65 per cent immature cells of the myeloid series. She was dismissed on the eighteenth day, improved.

Between that time and the day of her death, November 28, 1942, she was admitted to the hospital 13 times, for a total of 16 admissions. The clinical course was characterized by febrile episodes, severe anemia requiring repeated blood transfusions, and a terminal severe hemorrhagic diathesis. She developed jaundice once during this time, and her liver became enlarged and tender. At no time did she

have generalized lymphadenopathy. Her white count during the terminal 11 months of her illness varied between 1,250 and 16,600, and the blood study on the day of her death was as follows: 30 per cent hemoglobin, 1.74 million red blood cells, 7,000 white blood cells, 12 per cent mature neutrophils, 20 per cent myelocytes, 14 per cent myeloblasts, 8 per cent large lymphocytes, 42 per cent small lymphocytes and 4 per cent eosinophils.

Permission to perform an autopsy was not obtained.

Case 3. A 30 year old woman was seen by Dr. Harold F. Spencer at Emporia, Kansas, on November 30, 1946, complaining of progressive weakness, nausea and vomiting, pregnancy of three and one-half months, and the "flu" for the past month. She had taken thyroid tablets intermittently for years for "thyroid deficiency." Her only other pregnancy, six years earlier, had been uncomplicated. Her mother had died of carcinoma of the stomach at the age of 51; otherwise, her past and family histories were not remarkable.

Physical findings were those of a severe anemia. The temperature was 99.8° F. The blood findings were as follows: 23 per cent hemoglobin, color index 0.89, 1.31 million red blood cells, 3,200 white blood cells, 22 per cent neutrophils, 77 per cent lymphocytes, 1 per cent eosinophils, 160,000 platelets, and 1.1 per cent reticulocytes. Two sternal punctures for marrow study were done but, due to technical error, were unsatisfactory for examination. The sedimentation rate was 40 mm. in 20 minutes (Cutler), and the serum protein was reported as 4.09 gm. per 100 c.c., with an A–G ratio of 1–1. Two gastric analyses showed no free hydrochloric acid. Aplastic anemia was considered the diagnosis of choice, and transfusions, reticulogen and folic acid were given, with little improvement.

About six weeks later a differential leukocyte count was done by Dr. F. C. Helwig, with the following findings: 84 per cent myeloblasts, 7 per cent premyelocytes, 1 per cent neutrophilic myelocytes, 2 per cent band neutrophils, 2 per cent segmented neutrophils, 3 per cent small lymphocytes and 1 per cent large lymphocytes. A diagnosis of acute myeloblastic leukemia was made.

Marked hemorrhagic diathesis developed and repeated blood transfusions were given. She started labor spontaneously on April 9, 1947, during her eighth month of pregnancy, and after 22 hours delivered an apparently normal 4 pound 5 ounce premature girl. Moderate post-partum bleeding persisted for eight days, during which time she was given several transfusions.

The baby developed difficult breathing and started vomiting one day after birth and died on the fifth day. Autopsy showed only bronchopneumonia and fatty infiltration of the liver. No evidence of leukemia was found.

Seventeen days post-partum the mother developed severe left upper quadrant pain, and the spleen was palpable for the first time. She continued to have multiple hemorrhages from her mucous membranes and cutaneous ecchymoses, and died on August 4, 1947, about four months post-partum and 10 months after the onset of her illness. At no time did she have generalized lymphadenopathy, and the spleen became palpable only late in the course of her disease. In about 50 studies, the leukocyte count varied between a maximum of 9,850 and a minimum of 2,250, and the patient received a total of 68 blood transfusions. Autopsy showed the classic findings of myeloblastic leukemia. Figure 1 is a high power field showing marked myeloid cell infiltration of the liver.

Case 4. A 23 year old woman who was delivered of her first baby in September, 1945, at a Naval hospital made a slow post-partum recovery and three months later had left upper quadrant pain. Physical examination revealed a large spleen and a blood picture diagnostic of chronic myelogenous leukemia. Treatment consisted of the usual measures and roentgen-ray irradiation. Past and family histories were not remarkable.

About May, 1947, she became pregnant for the second time. A therapeutic abortion was considered but was refused by the patient. The attending obstetrician also felt that abortion was not indicated. No roentgen-ray irradiation was given during the pregnancy, and the patient went to term without complications.

She was admitted to this hospital on January 23, 1948, at term and in labor. The duration of labor was eight hours, and she was delivered of a normal 6 pound 13 ounce male. At this time she had no adenopathy, and the spleen was palpable

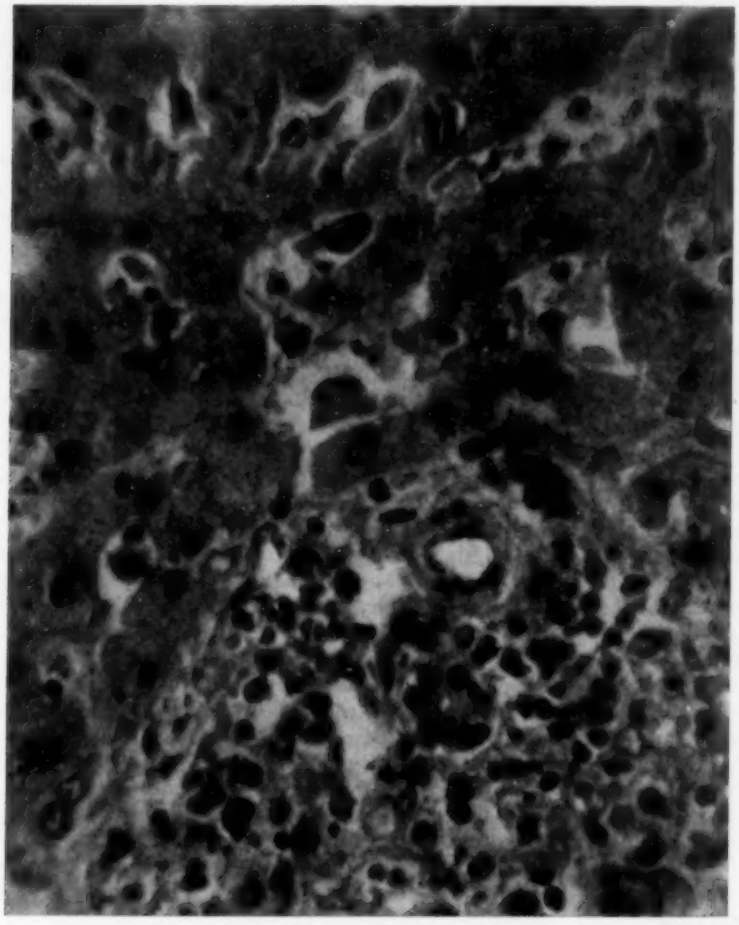

FIG. 1. High power field showing marked myeloid cell infiltration of the liver of case 3.

four fingerbreadths below the costal margin. Histologic examination of the placenta showed areas of focal calcification but no evidence of myeloid cell infiltration. The blood picture on admission was as follows: 56 per cent hemoglobin, 2.98 million red blood cells, 21,750 white blood cells, 33 per cent segmented neutrophils, 30 per cent band forms, 13 per cent juveniles, 9 per cent myelocytes, 3 per cent premyelocytes, 1 per cent myeloblasts, 6 per cent lymphocytes, 2 per cent monocytes and 3 per cent basophils.

Following delivery, mucous membrane and retinal hemorrhages occurred. Excessive uterine bleeding also occurred, necessitating multiple blood transfusions and a dilatation and curettage. She developed adenopathy, and roentgen-ray showed enlarged hilar glands. She improved somewhat and was dismissed on the twenty-ninth post-partum day.

She was re-admitted on March 1, 1948, five weeks post-partum, with widespread hemorrhages. The course was progressively downward, and she died on March 13,

FIG. 2. Low power field through the stomach wall showing gastric mucosa and a submucous nodule consisting of an accumulation of myeloid cells, case 4.

about seven weeks post-partum. During the last seven weeks of life, her white blood cell count varied between 21,750 and 79,000, the latter seven days before death.

Autopsy showed the classic findings of chronic myelogenous leukemia, with massive leukemic infiltration of the diaphragm, peritoneum, liver, kidneys, spleen, lymph nodes, lungs, meninges, involuting uterus and stomach wall. The spleen weighed 2,240 gm. and the liver 3,650 gm. Figure 2 is a low power field through

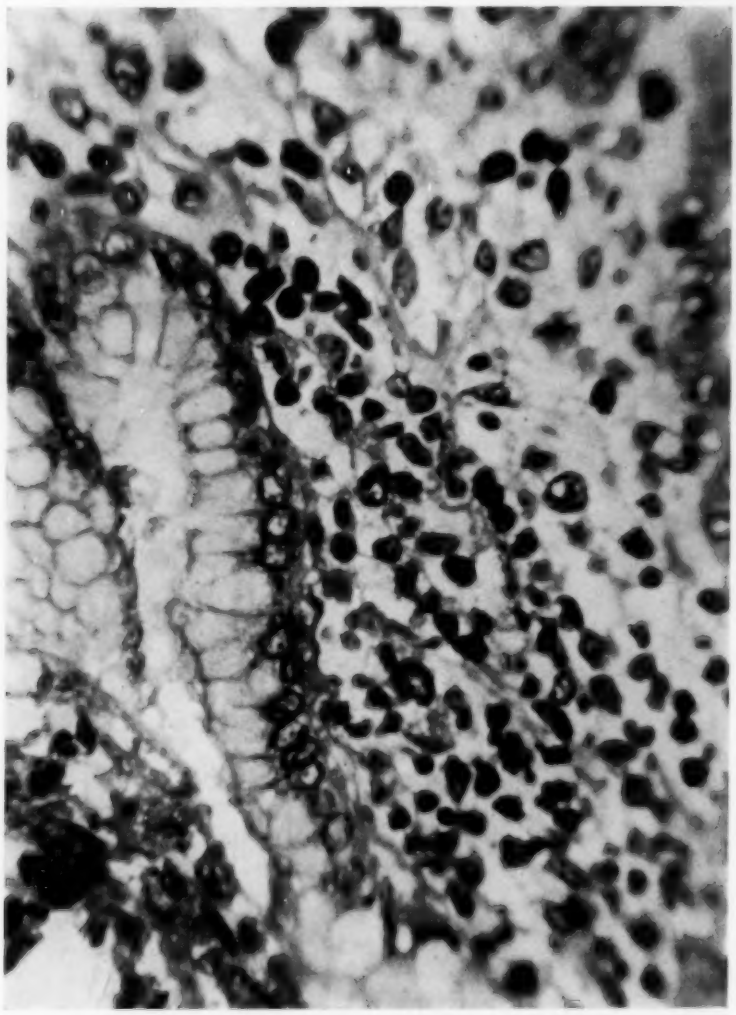

FIG. 3. High power field of same slide as figure 2.

an infiltrated area of the stomach, and figure 3 is a high power field of the same tissue. Figure 4 is a low power field through an area of infiltration beneath the dura, and figure 5 is a high power view of the same.

COMMENT

The vaginal bleeding which occurred when case 1 was six and one-half months pregnant may have been due to undiagnosed leukemia. However, the blood picture was not considered characteristic of leukemia on routine examination. Also, the patient's statement that her spleen had been enlarged three years previously may not be relevant. The total known dura-

tion of her leukemia was about 30 months, and during this time her two pregnancies, each interrupted by therapeutic abortion at about two and one-half months, apparently did not alter the course of the disease.

The leukemia in case 2 developed before or during the course of her pregnancy, although the diagnosis was made from a routine blood study

FIG. 4. Low power field showing dura mater with a mass of myeloid cells from subdural nodule, case 4.

at the time of her delivery. It is impossible to state the actual date of the onset, and the disease did not become symptomatic until after delivery. The total known duration of the disease was about 23 months, and the infant was normal.

The onset of the acute myelogenous leukemia in case 3 was during the first trimester of her pregnancy, and the course was characterized by severe

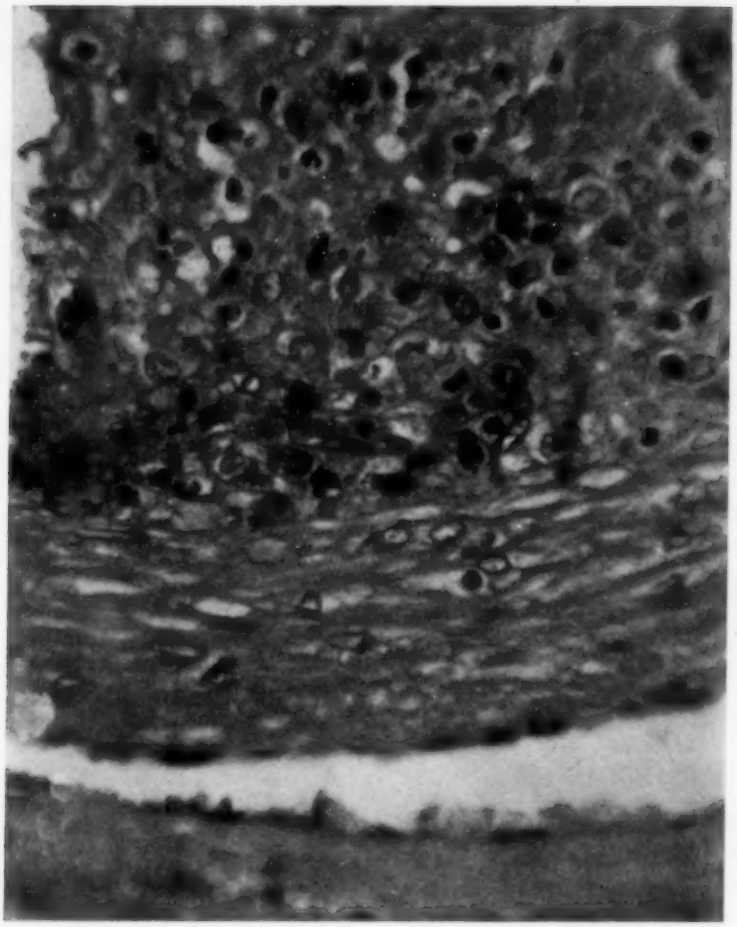

FIG. 5. High power field showing dura mater with subdural nodule made up largely of myeloid cells, case 4.

anemia, bouts of fever, bleeding and death 10 months after onset. The one month premature infant survived only a few days, and necropsy showed no evidence of leukemia in the offspring. The total duration of the disease, about 10 months, far exceeds the average life expectancy in acute leukemia.[4]

In case 4, conception occurred about 18 months after the onset of chronic myelogenous leukemia, and a normal living male was delivered at term. The mother died about two and one-half years after the onset of the disease and seven weeks post-partum.

DISCUSSION

Erf [1] summarized 100 cases of leukemia complicated by pregnancy. To these we wish to add our four cases and six others collected from the litera-

ture. These are listed in table 1. Bibliographic mention is made of two additional cases.[5, 6] These papers were not reviewed and were not classified in table 1.

It is not our intention to give a detailed review of the literature covering leukemia complicated by pregnancy; however, certain principles in the man-

TABLE I

Leukemias

Case	Author	Year	Age	Acute or Chronic	Relation of Onset to Gestation	Period of Gestation When Delivered	Death of Mother Post-partum	Child	Total Duration of Disease
1	Olmer[7]	1938	34	Acute	3d mo.	4+ mos. Induced	5 mos.?	Nonviable	36+ wks.
2	Jürgens[8]	1938	27	Chronic	6th mo.	8 mos.	2 hrs.	Died	12 wks.
3	Souper[6]	1938	Bibliographic mention only						
4	Lewit[5]	1946	Bibliographic mention only						
5	Harris[9]	1947	34	Acute	5th mo.	5 mo. aborted	19 wks.	Nonviable	20 wks.
6	Almklov[10]	1946	26	Acute	6th mo.	Not delivered	—	Died in utero	4 wks.
7	Williams[3]	1948	—	Chronic	7th mo.	Term-section	—	Lived	Over 1 yr.
8	Williams[3]	1948	35	Acute	6th mo.	Near term-section	Day of section	Lived	9 wks.
9	Slentz	1948	25	Chronic	7 mos. prior 23 mos. prior	3d mo. aborted 3d mo. aborted	— 6 mos.	Nonviable Nonviable	30 mo.
10	Slentz	1948	25	Chronic	Near term	Term	23 mos.	Lived	23 mo.
11	Slentz	1948	30	Acute	1st Trimester	8th mo.	17 wks.	Died	10 mo.
12	Slentz	1948	23	Chronic	18 mos. prior	Term	7 wks.	Lived	30 mo.

agement of and facts pertaining to these cases have evolved and are listed below for emphasis:

1. Interruption of pregnancy in a woman with any form of leukemia serves only to produce a premature or nonviable baby and the mother is not benefited.[2] Pregnancy has not been shown to alter the course of the leukemia, and interruption may even hasten the mother's death, especially in the acute forms. In the chronic forms, 75 per cent of the babies are normal, and there is little logic in sacrificing the life of the baby in the hope of prolonging the life of an already doomed mother!

2. Cesarean section is justifiable when near term to save the baby and when the mother is near death.[2] The leukemic mother tolerates delivery as well as operative procedures, and death from uterine hemorrhage subsequent to delivery is conspicuous by its rarity.

3. No form of therapy is effective in the acute cases, and in chronic cases the use of Fowler's solution, transfusions and roentgen-ray irradiation is indicated. High voltage roentgen-ray therapy should be used with caution, however, to avoid injury to the fetus. Some feel radiation should not be used.[11]

4. Leukemia has never been shown to pass the placental barrier, no matter on which side of the placenta the leukemia exists.[1, 3, 12] A leukemic mother has never been known to give birth to a leukemic child.

5. Leukemia in the mother is a definite cause of premature birth of the offspring.[3]

Summary

1. We have reported four more cases of leukemia associated with pregnancy, and collected six additional cases from the literature, to make a total of 110 reported cases.

2. Pertinent facts and principles have been listed.

Acknowledgment

We are indebted to Dr. H. F. Spencer, of Emporia, Kansas, and Dr. Paul A. Gempel, Dr. J. Milton Singleton and the late Dr. Ellis W. Willhelmy, of Kansas City, Missouri, and to the Kansas City General Hospital for permitting us to use the above cases as a basis for this report. We also wish to express deep appreciation to Dr. F. C. Helwig, pathologist at St. Luke's Hospital, for his advice and encouragement in the preparation of this paper.

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A CLINICAL STUDY OF MALNUTRITION IN JAPANESE PRISONERS OF WAR*

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DURING World War I the famine and starvation that occurred in certain parts of central Europe prompted some studies,[1, 2, 3] particularly concerning the associated edema. The events of World War II, especially the lengthy periods of starvation that occurred in various prison camps, further stimulated numerous researches on the effects of starvation in the human subject.[4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23] The majority of these studies centered their attention on the edema, but a few included such phases as the burning feet syndrome, the neuropathy, the amblyopia and the hematologic changes. Despite some puzzling facts concerning the edema of war famine,[24, 25, 26] at the beginning of World War II it was still generally held that an inadequate diet led to protein deficiency, which in turn decreased the colloid osmotic pressure of the blood, with resulting edema. Also considered to be of great importance in the picture, particularly with reference to pains in the legs, was vitamin B_1 (thiamin chloride) deficiency. Several careful metabolic studies [27, 28, 29, 30] have thrown much light on the mechanisms involved in famine edema, but there still are important questions left unanswered, as emphasized by Beattie and his associates.[29, 30] It is the purpose of this report to place on record rather extensive clinical data that were accumulated in a special study in a Japanese prison camp in the Philippine Islands in the fall of 1945.

With the defeat of the Japanese in the Philippine Islands during the spring of 1945, their armies began to retreat into the hills of Luzon. There they had to separate into small groups for food, pilfering as they went. Hence, April, May and June of 1945 brought increasing starvation to the Japanese, who had to live chiefly on such substances as grasses, leaves, and potato tops. The usual rice, sugar cane, carabao meat and vegetables were kept from them by the Filipinos. Thousands of Japanese developed malaria, dysentery and edema during this period, and many died.

After V–J day, September 2, 1945, Japanese troops began to surrender by the thousands, so that by early October approximately 80,000 had been confined in New Bilibid Prison. With this the 174th Station Hospital, a 250-bed installation at New Bilibid Prison, was suddenly overwhelmed with the care of 5,700 of these prisoners, many of whom were too ill to move from their cots. An organization was quickly set up utilizing captured

* Received for publication December 2, 1949.

Japanese doctors, nurses and ward men to care for these patients under the supervision of American medical officers.

This circumstance brought about a most unusual spectacle of severe starvation in the human subject in its various stages and manifestations. The pitiful physical state of these individuals immediately stimulated interest to make certain observations and to carry out treatment.*

Nature of the Material

From a scientific standpoint it would have been highly desirable to carry out detailed balance studies, including vitamin assays, and to institute experimental treatments and study their results. The observations had to remain clinical, however, for four reasons. First, it was the Government's plan to evacuate all these patients to Japan by January 1, 1946. The group was permitted only six weeks in which to make its observations. Second was the difficulty in selecting enough well qualified medical officers who could be spared from Military Hospital duty. No one was found who was qualified to do vitamin assays. Third, there was a shortage of special medicaments such as amino acids, injectable vitamin preparations, and other items needed for clinical therapeutic research. Fourth, we were instructed that the rules of the Geneva Conference provided that no experimentation could be carried out on any prisoners. We could treat them, make observations and record our results. At the same time, we were not allowed to show any partiality to the group of cases selected. We had to give the same diet and medicaments to a final total of 8,000 patients that we gave to the special group under study, thereby limiting the amount of vitamins and medicines available for the special group.

However, subject to these restrictions, it was agreed to select for special study a small group of the most severely starved patients. Twenty-four cases were selected, 12 with massive edema (so-called "wet" beriberi) and 12 with no edema (so-called "dry" beriberi). Care was taken not to include any victims of tuberculosis or other chronic debilitating diseases that might simulate or aggravate the effects of starvation. These 24 patients were placed in a special ward staffed by Japanese personnel and given ordinary good medical care, including a diet of 3,400 calories, which contained 12 ounces of meat per day and citrus fruit juices, and which was supplemented by 24 yeast tablets, 10 mg. of thiamin chloride and 15 gr. of ferrous sulfate by mouth daily.

The study included a history with special emphasis on diet, complete physical examination, routine laboratory studies before, during and after treatment, and certain special procedures of interest in malnutrition. Any

* Through the efforts of Brig. Gen. Jos. I. Martin, Chief Surgeon, AFWESPAC, Brig. Gen. Hugh J. Morgan, Chief Medical Consultant, and Col. Francis R. Dieuaide, Consultant in Tropical Diseases, Surgeon General's Office, Washington, and Col. Roy H. Turner, Medical Consultant, AFPAC, a ward for special studies was set aside and an outline of investigation and care for these patients was formulated.

patients in this group who died were to have complete postmortem examination performed. Since a representative picture of malnutrition was desired, it was planned that if very few in this group died, autopsies were to be performed on several other fatal cases of starvation not especially studied.

For controls, 24 apparently healthy Japanese ward boys were selected for physical examination and certain laboratory studies to compare with the group under investigation.

Clinical Findings

All the patients were males ranging in age from 21 to 49 years. Patients number 1 through 12 were labeled "wet," and patients number 13 through 24 were labeled "dry." Any replacements for those who died received the same numerals, followed by an "A." There were four deaths with three replacements, two in the wet group and one in the dry. The fourth patient, a dry case, died so near the end of the study that a replacement was not made.

History

All histories were obtained through two Nisei interpreters, under instruction of Captain Arthur L. Ruby and one of us (P. M.). Although the patients had so recently been enemies, their full coöperation was quickly obtained.

As has been stated, the period of their starvation began in March, 1945, and continued through September, a period of five to six months. Their diet, from rough estimation, had averaged 800 to 1,000 calories, often less. We were unable to make any reasonable estimate of the amount of protein, vitamins or salt intake prior to capture.

The onset of symptoms was gradual and insidious except in nine patients (three wet and six dry), in whom it was abrupt following an attack of malaria. Approximately three-fourths of the patients gave a history of malaria and about two-thirds a history of diarrhea prior to capture, about equal in the wet and dry groups. Marked weakness was a universal complaint, and it was, as a rule, the initial one. Twelve patients (four wet and eight dry) were so weak that they were bed-fast on admission. Loss of appetite was a common early symptom. It was present in eight of the wet cases and 11 of the dry.

Marked loss of weight was a uniform finding, in the wet cases as well as in the dry. The patient's statement of his former measured body weight was accepted, but estimates were not. The average weight of these patients in health was about 110 to 120 pounds. The average weight of the dry group upon admission, and of the wet group after loss of edema, was about 75 pounds. Thus the loss of weight was about 40 to 50 pounds per person, or approximately 40 per cent of body weight.

Edema occurred not only in all of the wet cases but also at some time in 10 of the dry cases. Of the final number of 13 cases in the dry group,

nine had had edema before capture and one developed edema by the end of the study. Only three of the 13 dry cases showed no edema at any time. Edema, when marked, was usually associated with palpitation, dyspnea on exertion and postprandial epigastric fullness. It became very apparent in the history that oliguria was the rule as the edema accumulated and that polyuria occurred as it receded.

FIG. 1. A typical "wet" case. The edema is generalized, including the genitals.

Only two in each group complained of mild disturbances of vision. None had night blindness. One of the dry cases and eight of the wet cases complained of some diminution of hearing. Five in the dry group and one in the wet group gave a history of sore tongue. Two, one in each group, had cheilitis.

All of the patients in the wet group gave a history of dyspnea and palpitation as a major complaint. In contrast, one-third of the dry group had such symptoms, and only on exertion. None gave a history of anginal pain or cough.

Most of the patients complained of anorexia, aggravated by malaria or diarrhea; in the wet group, particularly those with ascites, many complained

of a full feeling following the ingestion of only a mouthful of food. None gave a history of nausea or vomiting. Five of the dry group had had periodic episodes of lower abdominal cramps. Diarrhea was complained of in seven of the wet cases and in 11 of the dry cases.

None complained of any significant urinary symptoms. Two or three gave a history of transient hematuria, and one patient had possibly had an attack of renal colic.

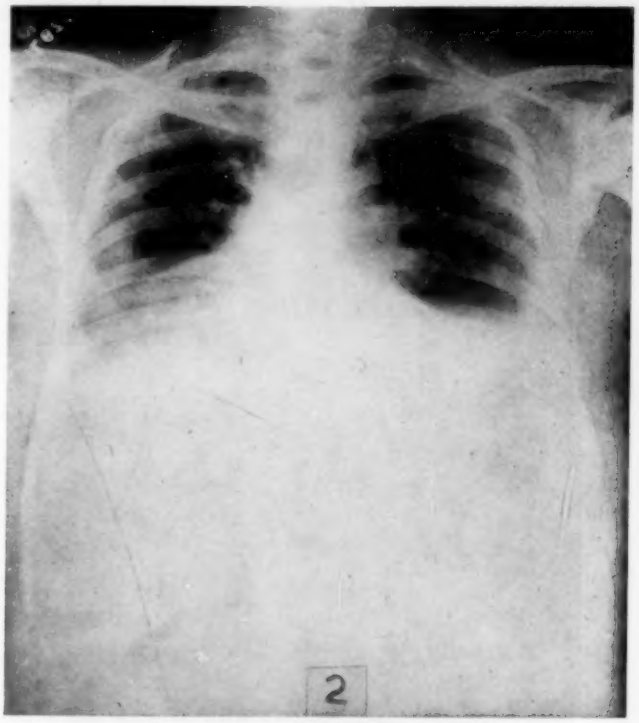

FIG. 2. A roentgenogram of the chest from a "wet" case.

It seemed to us remarkable that only a few (five of the wet and eight of the dry cases) gave a history of subjective neurologic symptoms, numbness, tingling and weakness of the lower extremities. Nearly all of the patients, however, did complain of heaviness of the legs when edema was present. No instance was encountered of the "burning feet syndrome" described often in the recent literature on malnutrition.[4, 12, 18, 19, 20]

From the standpoint of a detailed history, it was rather striking how few gave any clear-cut history of vitamin deficiency, such as visual disturbances, sore mouth or tongue, or neurologic manifestations. Rather, their chief symptoms were of illnesses such as diarrhea and malaria, and weakness, dyspnea, anorexia, and heaviness of the legs with edema.

Physical Findings

All the patients were in such poor physical state that they were at first confined to bed. Three in the wet group and six in the dry group were unable to sit up unaided.

Edema. The 12 patients in the wet group had "moderate" to "very marked" edema. It was most pronounced in the abdomen and lower extremities. In all cases it was of the soft, pitting type. Two of these required abdominal paracentesis. Many had myoedema with pitting of the

Fig. 3. A typical "dry" case, showing the severe degree of malnutrition.

skin surface. A third of this group had edema of the genitalia. Several had edema of the face and hands. Only three in this group did not have pleural effusion, but they all had pulmonary congestion. A typical example of a wet case is shown in figure 1. Figure 2 illustrates the usual roentgenogram of the chest in one of this group.

In contrast, the patients in the dry group looked like "skin and bones." As has been mentioned, practically all of the patients in this group had given a history of variable edema before hospitalization. At the time of selection, however, and on initial examination, only three had 1 plus edema that was limited to the feet. Figure 3 shows a typical example of a dry case. Only

one of this group had slight pleural effusion. The remainder had a roentgenogram of the chest such as is shown in figure 4.

Skin. Examination of the skin usually disclosed a dry, loose and atrophic integument except when tense over edematous areas. Five in the dry group and one in the wet group had scabies. In both groups, about half of the patients showed a hyperkeratotic "goose flesh" skin, particularly over the abdomen and anterior aspects of the thighs. This suggested vitamin A deficiency, but it was remarkable how well the skin cleared up in a few

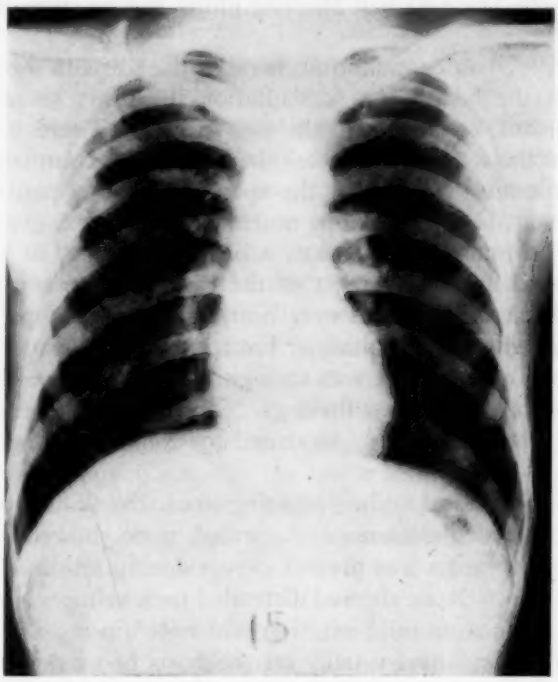

FIG. 4. A roentgenogram of the chest from a "dry" case.

days with soap and water. No distinct pellagrous lesions were seen. Over edematous regions there appeared numerous areas of brown mottling with scaling, more noticeable as the fluid disappeared. There were a few instances of trichophytosis. Three of the wet and two of the dry cases had decubitus ulcers. Others (all in the wet group) had ulcerative lesions of the extremities. Patient 18 had an eczematous, weeping, generalized eruption. A most unusual finding occurred in three patients in the dry group; a peculiar uniform orange (nicotine stain color) discoloration of the nails of both hands and feet. Its significance was not at all clear. As the nails grew out a normal appearing structure appeared, the nicotine discoloration advancing distally. In general, the condition of the nails was good.

The *eyes,* including ophthalmoscopic examination, were negative except for pallor of the conjunctivae, and in two cases (one in each group), conjunctivitis.

One wet and two dry cases had discharging *ears,* all three with old perforations of the drum.

Most of the patients showed some degree of marginal papillary atrophy of the *tongue.* One case in the wet and three cases in the dry group had severe atrophy and marked reddening, with a magenta color in one.

In general the *teeth* were in bad condition but were adequate for mastication. Only one (case 8) had bleeding gums, but no sponginess to suggest scurvy.

The Heart. Upon examination, none of the patients showed significant enlargement of the heart. On auscultation the heart sounds were rather impure and distant, equally so in the two groups. There was some accentuation of P_2 in the wet group, a few others with A_2 accentuated, and several with distinct diminution of S_1 at the apex. Only one patient (in the wet group) had a soft, blowing systolic murmur at the apex, grade II, that was considered to be functional. It was a little surprising, in the presence of the anemia found later, that most of the cases had no murmur whatever. No pericardial friction rub was ever heard in either group. No diagnosis of valvular heart disease was made. Except for the increased P_2 in the wet group mentioned above, there was no significant difference between the wet and dry groups in their cardiac findings. The pulse usually was quite labile. It was noted to be considerably increased by even slight exertion, and with fever.

There was no physical finding pointing to cardiac failure, as with beriberi heart, as the cause of the edema. As stated, none showed cardiac enlargement, and no tachycardia was present except during febrile episodes or with attempted exertion. None showed distended neck veins. No gallop rhythm was heard. Dyspnea on mild exertion was noted in most of the wet cases, but this could be explained usually on the basis of marked ascites and the collection of fluid in the pleural cavities. None was orthopneic, all could lie flat. No instance of bradycardia was found.

The *blood pressure* was normal to low in most instances, a little higher on the average in the wet group. To state it in another way, according to our American standards the patients in the wet group had normal blood pressures, 100 to 130 mm. mercury systolic, 60 to 90 mm. mercury diastolic. In contrast, the patients in the dry group had lower blood pressure readings, average 80 to 105 mm. mercury systolic and 50 to 85 mm. mercury diastolic. Parenthetically it should be remarked that the 24 control subjects had, for the most part, low blood pressures, with systolic readings of 80 to 100 mm. mercury and diastolic levels of 45 to 80 mm. mercury. Thus, compared with the controls, the blood pressure was normal in the dry and high in the wet group.

The *lungs* revealed no abnormality except the pleural effusion or congestion in the wet group.

In the *abdomen,* ascites was present in all of the wet group in sufficient amount to preclude palpation of abdominal masses. As the ascites subsided, an enlarged, nontender liver was found in two of the wet cases, but the spleen was not felt in any patient in either group. One patient (case 16) developed abdominal pain and tenderness during the first few days of the study and died from peritonitis due to rupture of an amebic ulcer of the bowel.

The *genitalia* were negative except for edema in the wet cases.

There was no significant lymphadenopathy in the series except in case 16A, in whom there was mild generalized glandular enlargement, particularly in the groins. Roentgenograms showed mediastinal enlargement, presumed to be due to glands, in case 21, but there was no associated regional adenopathy. The cause of these enlargements was not determined.

Neurologic Findings. In the course of accumulating the data there occurred many variations in the neurologic findings as recorded by different observers on different occasions. Such disturbances of sensory and motor function as were found occurred chiefly in the lower extremities. Four of the patients, one in the wet and three in the dry group, showed diminution of pain sensation in the feet. Two of these in the dry group also had some loss of tactile sensation in the thighs. Eight other patients (five in the wet and three in the dry group) were recorded as having some loss of tactile sensation with loss of pain sense in the lower legs. One of these (case 17 in the dry group) showed a stocking area of hypesthesia reaching to the midthigh bilaterally. In no case was vibratory sensation lost, although several in both groups showed a transient diminution to the tuning fork test. Position sense was normal in all.

Although all patients showed generalized muscular wasting, no frank paralysis was encountered. One patient in the wet group had distinct weakness of the calf muscles. Five patients in the dry group were recorded as showing weakness in the quadriceps groups of muscles. No distinct peroneal involvement was found. A few in the dry group presented what appeared to be disproportionate atrophy of the interossei and the thenar and hypothenar eminences of the hands. Muscular fibrillary twitchings were not observed in any patient. In the deep tendon reflexes also there was much variation. In nine of the cases (six wet and three dry), the reflexes were always active and brisk. In the remainder the findings were quite variable, sometimes active, at other times sluggish, with a slight tendency toward improvement during the period of observation. In no case were deep tendon reflexes persistently absent. All had active abdominal and cremasteric reflexes. None showed a positive Romberg or Babinski sign.

Laboratory Findings

At the beginning of the study all laboratory procedures were done as expeditiously as possible for comparison with later data. Certain of the more important observations were repeated at weekly intervals, others were done only at the beginning and at the end of the six weeks' study. To avoid lengthy tables and to conserve space table 1 has been drawn up giving the initial figures (average) at the beginning of the study, with the variations in parentheses, and the final figures for comparison.

TABLE I

Laboratory Data

(Average values. The range is given in parentheses)

	Initial Values		Final Values		Controls
	Wet	Dry	Wet	Dry	
Hemoglobin	9.3 gm. (6.8–13.2)	8.6 gm. (6.5–12.6)	10.6 gm. (8.2–14.2)	9.4 gm. (7.0–11.4)	14.7 gm. (13.2–16.8)
Red blood cells	3.42M (2.11–4.36)	2.80M (1.76–3.80)	3.64M (2.9–4.0)	3.27M (2.7–3.8)	4.66M (4.3–5.2)
White blood cells	7,810 (3.5–22.3)	7,425 (2.6–15.9)	11,050 (9.0–12.7)	10,740 (8.0–14.2)	8,200 (6.1–14.4)
Hematocrit	32% (21–44)	27% (16–41)	34% (27–44)	31% (25–36)	43% (33–49)
Mean corp. vol.	93 (59–115)	99 (84–124)	92 (83–103)	101 (79–116)	85 (79–92)
Mean. corp. hem.	29 (21–38)	31 (26–37)	30 (23–36)	30 (25–37)	32 (31–33)
Mean. corp. hem. conc.	30 (21–37)	31 (30–35)	32 (28–35)	31 (28–34)	34 (32–36)
Blood sp. gr.	1.0412 (1.036–1.051)	1.0397 (1.034–1.046)	1.0461 (1.039–1.054)	1.0430 (1.037–1.048)	1.0572 (1.054–1.061)
Sed. rate	34 (7–64)	37 (11–76)	39 (15–56)	54 (38–65)	24 (4–50)
Cholesterol	122 mg. (75–256)	79 mg. (62–107)	143 mg. (108–197)	125 mg. (81–181)	126 mg. (80–183)
Whole blood chloride	464 mg. (437–487)	463 mg. (439–485)			not done
Urinary creatine	0.530 gm. (0.223–0.850)	0.420 gm. (0.103–0.648)			not done
B.M.R.	−10 per cent (+8.5 to −23.5)	−7 per cent (+7 to −15.5)			not done
Circ. time	13.5 sec. (12.0–18.5)	13.5 sec. (10.0–17.5)			not done
Venous pressure	110 mm. (44–190)	93 mm. (40–138)			not done
Thymol turbidity	12.3 units (5.0–19.0)	10.3 units (5.0–19.0)	14.0 units (8.0–19.0)	14.8 units (8.0–21.0)	10.0 units (4.0–16.0)
B.S.P.	4.0 per cent (1.0–8.0)	1.9 per cent (0.0–7.5)	3.1 per cent (0.0–7.5)	1.3 per cent (0.0–3.5)	not done
P.S.P.	36 per cent (20–50)	47.5 per cent (15–70)	57 per cent (40–97)	48 per cent (42.5–62.5)	not done

Hematology. The following studies were performed at weekly intervals, using methods standard in the Army during World War II (T.M. 8–227): hemoglobin by the specific gravity method using copper sulfate; red blood cell, white blood cell and differential counts using finger blood in the usual manner; blood sedimentation rate by the method of Wintrobe. No correction was made for anemia. Blood hematocrit by centrifuging a Wintrobe tube one-half hour at 3,000 r.p.m.; blood specific gravity was done by the drop method using copper sulfate solution. Bone marrow studies were not performed.

All of the patients, when contrasted with the Japanese control subjects, had a moderate to severe degree of anemia. The type and degree of anemia had to be evaluated from the red blood cell counts, hematocrit, mean corpuscular volume and the smears, for the other studies, showing lowered total plasma proteins, invalidated the drop method in copper sulfate for hemoglobin estimations. In the same way, the data regarding the mean corpuscular hemoglobin and the mean corpuscular hemoglobin concentration are inaccurate, but the figures for mean corpuscular volume appear to be adequate.

The types of anemia and their relative lack of response to treatment during the six weeks of observation are shown in table 2. The figures are based on mean corpuscular volume determination.

TABLE II

Types of Anemia

	Initial Values			Final Values		
	Wet	Dry	Total	Wet	Dry	Total
Macrocytic	7	8	15	4	5	9
Normocytic	4	4	8	5	2	7
Microcytic (hypochromic)	1	0	1	1	3	4

In addition to inadequate intake of food and iron, malaria and the presence of intestinal parasites certainly contributed to the production and persistence of the anemia. During the course of therapy with ferrous sulfate, 5 gr. three times a day, 14 cases (eight wet and six dry) showed some improvement; six cases (two wet and four dry) showed a drop in all values, and in the remaining four the results could not be ascertained because of death. One patient in the wet group changed from a slight macrocytic anemia, with repeated debilitating attacks of falciparum malaria, to a marked microcytic anemia. Two cases, one wet and one dry, changed from a picture of macrocytosis to a normocytosis without significant change in the red blood cell count. No liver or folic acid or whole blood transfusion was given; no reticulocyte count was done during the iron therapy.

A study of the blood *leukocytes* showed essentially normal total counts at the beginning of the study, with slight elevation at the end of the period of observation. A phenomenon curious to us occurred in many instances during an attack of malaria. Whereas in our American soldiers a leukopenia usually occurred with malaria, in these Japanese prisoners a leukocytosis as high as 12,000 to 14,000 cells per cu. mm. frequently developed. During the course of the study the polymorphonuclear leukocytes averaged about 70 per cent and the lymphocytes approximately 21 per cent. Several showed a monocytosis of 4 to 7 per cent.

Despite the almost universal incidence of intestinal parasites in these patients, only seven (five in the wet and two in the dry group) showed an eosinophilia over

5 per cent. These cases (two wet and one dry) showed values of 19, 10 and 19 per cent, respectively. The eosinophilia had disappeared in all cases (only one showed 2 per cent and two showed 1 per cent) by the end of the study, even though no antiparasitic treatment had been carried out and the intestinal worms or ova were still found in nearly all stools.

At the beginning of the study the values for blood specific gravity were lowered below the normal of 1.052 to 1.055 in all the cases, equally so in both wet and dry groups. By the end of the study there was but very slight improvement, the average reading being about 1.040. The values in the control subjects averaged 1.057.

Blood Proteins. The blood serum total proteins, albumin, globulin and albumin-globulin ratios were determined on each patient at weekly intervals. The procedure employed was the method of Kingsley,[31] with normal total protein values 6.5 to 8.0 gm., albumin 4.5 to 6.5 gm., globulin 1.5 to 2.5 gm. per 100 c.c., and an A–G ratio of 2.0 to 2.3.

TABLE III

Blood Protein Studies

(Average values; the range is given in parentheses)

	Initial Values		Final Values		Controls
	Wet	Dry	Wet	Dry	
Total protein	4.48 gm. (3.4–5.3)	4.75 gm. (4.0–6.1)	4.92 gm. (3.7–6.6)	4.88 gm. (3.9–6.1)	6.98 gm. (6.4–7.6)
Albumin	1.96 gm. (1.5–2.5)	1.87 gm. (1.4–2.4)	2.07 gm. (1.1–3.4)	1.92 gm. (1.3–3.1)	4.47 gm. (4.0–4.8)
Globulin	2.51 gm. (1.8–3.3)	2.77 gm. (2.4–3.8)	2.85 gm. (2.1–4.1)	2.94 gm. (2.4–3.5)	2.58 gm. (2.0–3.8)
A/G ratio	0.810 (0.54–1.08)	0.675 (0.44–0.96)	0.716 (0.35–1.36)	0.662 (0.38–1.35)	1.81 (1.2–2.4)

Since the blood proteins constituted a most important element of the study, the results are tabulated separately in table 3. In the initial studies all values were lowered. Repeated determinations to the end of the study showed a slight but definite rise in nearly all elements in both groups. However, there was no remarkable improvement during the period of observation. In fact, in no case in either the wet or the dry groups did the blood proteins return to normal levels after six weeks of adequate protein feeding.

In a careful examination of all the blood protein studies no significant difference was detected between the wet and the dry groups. Even the three cases in the dry group who never showed edema (16A, 22 and 23) were equally hypoproteinemic.

Studies of the 24 Japanese controls showed values resembling normal American standards for blood proteins, with an average total protein of 6.98 gm. per 100 c.c., albumin 4.47 and globulin 2.58 gm. per 100 c.c.

Blood Cholesterol. These studies were performed using a modified method of Sperry [32] in which the normal values for Occidentals range between 140 and 190 mg. per 100 c.c. However, it has been noted by Snapper [33] that blood cholesterol levels are somewhat lower in Orientals. We found low values also in our control series, average 126 mg. per 100 c.c.

In comparing the two groups under study, the average value in the wet group was similar to that in the controls, but the range was wider, reaching as high as 256

mg. per 100 c.c. The average pretreatment value for cholesterol in the dry group was much lower than in the controls. Early in the course of treatment the cholesterol level fell in some cases, and in case 19 it reached a nadir of 46 mg. per 100 c.c. By the end of treatment the cholesterol level in the dry cases was similar to that in the control group.

Blood Chlorides. The profound weakness seen in these patients made determination of the plasma sodium and chloride advisable to investigate the possibility of Addison's disease and of hyponatremia and hypochloremia due to other causes. Facilities were not available for doing sodium studies, but whole blood chlorides were determined in all cases using the standard silver nitrate method. Normal values range from 450 to 500 mg. per 100 c.c. Such procedures as the Kepler-Power water test to detect early Addison's disease were not carried out.

TABLE IV

Glucose Tolerance Tests

Patient No.	Fasting	30 min.	1 hour	2 hour	3 hour
(wet) 1	66 mg.	50 mg.	180 mg.	180 mg.	197 mg.
2	77	113	117	115	97
3	89	126	186	121	80
4	74	101	131	97	80
5	73	97	98	136	124
6	79	130	136	150	84
7	71	107	110	72	71
8	83	91	98	97	79
9	86	89	93	90	84
10A	71	116	138	156	143
11	84	106	133	147	130
(dry) 13	79	169	176	229	208
14	93	115	117	126	132
15	87	116	143	190	186
16A	63	115	143	156	88
17	66	107	108	97	94
18	73	88	91	111	83
19	73	112	125	167	150
21	63	90	107	124	130
22	67	122	143	122	125
23	85	153	170	134	115
24	73	88	111	96	122

In nearly all cases in both groups the whole blood chloride values were well within normal limits. Three in the wet group and two in the dry had values between 437 and 449 mg. per 100 c.c., but these were not considered of any significance. Because of these normal findings, determinations of blood chlorides were not carried out in the control subjects.

Blood Sugar. Oral glucose tolerance tests were done on all patients except two. Patient 12A in the wet group could not tolerate the sweet drink, and patient 20 in the dry group died the day before the tests were scheduled to be done. The standard method of Folin and Wu was used, giving 100 gm. of glucose by mouth after taking a fasting sample of venous blood and collecting further blood specimens at 30, 60, 120 and 180 minutes. The normal fasting values by this procedure are 80 to 120 mg. per 100 c.c. of blood. Tests using the intravenous administration of sugar were not carried out.

Since composite curves do not show the marked variations that occurred in both groups of cases, table 4 is given to show all of the blood sugar values in all cases tested.

Three cases in the wet group and three in the dry presented curves that usually are considered to be of a normal type. Four in the wet group and three in the dry had "flat" curves, that is, the peak value never rose above 120 mg. per 100 c.c. of blood. Four cases in the wet group and five in the dry had a delayed rise in the peak level, that is, to the second or third hour, with a value as high as 208 mg. per 100 c.c. at the third hour in case 13. None of the latter cases experienced nausea to suggest delayed emptying from the stomach. The fasting blood sugar was below 95 mg. per 100 c.c. in all cases and usually ranged between 60 and 80 mg. per 100 c.c. No instance of diabetes mellitus was found in the series. The type of curve presented by case 13 suggested diabetes, but at no time did this patient show glycosuria. Circumstances did not permit repetition of the glucose tolerance tests at the end of the study.

Blood Serology. The routine serologic test for syphilis that was used (Kahn) was negative in all cases except patients 8, 10A and 11 in the wet group. No quantitative tests were done.

Urine. Three routine urinalyses were carried out on each patient; additional examinations were done as indicated. The values for specific gravity were within normal limits but varied considerably with urinary output. The values were particularly high in the wet group: with edema present with oliguria, 1.028 to 1.032; with diuresis and loss of edema, 1.002 to 1.006. In the dry group the specific gravity ranged usually between 1.012 and 1.024. Albuminuria was unusual, never greater than 1 plus, and then transient, in the wet and dry groups equally. There were occasional instances also of 1 plus glycosuria, again transient, in both groups. As already stated, no instance of diabetes mellitus was encountered. A few cases in both groups showed 2 to 4 red blood cells per high power field of centrifuged urine, to be negative later on subsequent examination. Occasional patients also showed many white blood cells in the urine that disappeared later. After careful consideration, no diagnosis of nephritis was made in either group.

Creatine in the Urine. In males an increase in the excretion of creatine in the urine usually is associated with muscular wasting. Because of the severe muscular wasting found in this group of individuals, determinations of 24 hour urinary excretion of creatine were done, using the method of Hawk and Bergeim.[24] By this procedure the normal urinary creatine excretion is 0 to 0.100 gm. per 24 hours.

Two patients (12A in the wet group and 16A in the dry) showed very slight elevations. Eleven cases in the wet group and nine in the dry had values well over 0.200 gm., and some as high as 0.85 gm. per 24 hours. The average creatine excretion in the wet group was 0.53 gm., and in the dry group 0.420 gm. per 24 hours. Rather marked creatinuria was present equally in the wet and dry groups. These tests were performed at about the middle of the study and were not repeated.

Stools. At least four freshly passed stools from each patient were examined on a warm stage for *E. histolytica* or ova and other parasites. In addition, each patient had a proctoscopic examination, at which time mucosal smears were taken from suspicious areas, if present, and were examined immediately at the bedside for amebae on a warm stage microscope by several observers. It is of interest that no specimen was found to contain amebae at any time. However, case 16 in the dry group died early in the study of amebic peritonitis. Stool studies had been negative for amebae but a proctoscopic examination had not been made.

Seven-eighths of the patients, equally distributed in both groups, had ova of intestinal worms present. Thirteen patients showed the ova of *Ascaris lumbricoides,* 11 had *Necator americanus,* eight had *Trichuris trichiura,* and three had *Strongyloides.* One patient in each group had *Giardia lamblia.* Of the 22 patients who had intestinal parasites, 12 had a single infestation, six had two, two had three, and two had four different parasites present.

Three bacteriologic cultures taken from rectal swab smears were done on each patient. All cultures were negative for the typhoid, paratyphoid and dysentery groups of organisms, with the exception of three cases which had, respectively, *Shigella paradysenteriae*, Boyd P 274 (case 5); *Salmonella enteriditis* (case 21), and *Shigella paradysenteriae*, Boyd P 275 (case 24). In cases 5 and 24 the cultures were positive only once; in case 21 they were positive twice.

From an examination of the stools a diagnosis of sprue could not be made in any case. Unfortunately, facilities did not permit barium meal motor studies of the small intestines to be carried out.

Special Studies

In a study of this kind, a few special examinations were desirable in an attempt to throw further light on the problem.

Basal Metabolic Rate. Numerous studies during starvation in the past have shown a marked lowering of the basal metabolic rate. In this study the determinations were performed at the bedside, in the fasting state, with a Sanborn waterless apparatus. The weights recorded at the time of the tests were with or without edema, as the case happened to be; no correction was made for the edema.

Nearly all cases gave readings in the minus zone. In the wet group the readings averaged about minus 10 per cent, with only two cases showing plus readings, case 3 a plus 8.5 per cent and case 11 a plus 5 per cent. In the dry groups the readings were not quite so low, probably due to difference in surface area, with an average of minus 7 per cent. Again, only two cases showed plus readings, case 13 a plus 7 per cent and case 18 a plus 2.5 per cent. No determination of basal metabolic rate was done on the control subjects.

Heart and Circulation. A study of the heart size by 6 foot roentgenograms revealed no instance of gross cardiac enlargement. Early in the study it was impossible to measure the cardiac borders in the wet group because of the presence of pleural effusion. Later, when they could be measured, the hearts in the wet group were all normal in size. In a comparative study, the hearts in the wet cases were slightly larger than those in the dry group but, interestingly in both groups, they were smaller by measurement than in the controls. Abnormalities of cardiac contour were not encountered. Parenthetically, there was no instance of pulmonary parenchymal disease seen by roentgenogram in either group.

Circulation Time. The circulation time, arm-to-tongue, was performed by the intravenous injection of 10.0 c.c. of 10 per cent calcium gluconate, once repeated, determining the end-point with a stop watch. The results were all normal, that is, 12 to 18 seconds, except in one patient in the dry group, who had a circulation time of 10 seconds. There were some wide variations in single tests but at some time all showed normal values.

Venous Pressure. Measurements of venous pressure by the direct method, using a spinal manometer, showed rather marked variations. The readings varied for the most part between 50 and 150 mm. of water. In the wet group six patients had readings over 100 mm. of water, five showing such readings in the dry group. There was a tendency to slightly higher readings in the wet group than in the dry.

Electrocardiograms. The standard limb leads and precordial leads CF_1 to CF_6, inclusive, were taken on each patient with a Sanborn cardiette. For the most part the electrocardiograms were well within normal limits, a few showing low voltage and minor T wave changes. There was no difference between the two groups. Low voltage, particularly in the limb leads, was observed in five cases in the wet group and two in the dry group. Of these, two in each group also showed relatively low voltage in all of the precordial leads. There was no increase or abnormal shortening of P–R or QRS conduction. Bizarre forms were not observed. The T-wave changes

consisted of flattening, with only occasional slight inversion, seven in each group showing such changes.

Upon the usual inspection of the tracings it appeared in a few that there might be slight prolongation of the Q–T interval. Careful measurements, however, revealed the majority to be well within normal limits. The Q–T ratios determined by the nomographic method of Goldberger [35] revealed values that ranged between 0.82 and 0.16 in the wet group and between 0.80 and 1.15 in the dry group. Six cases, three

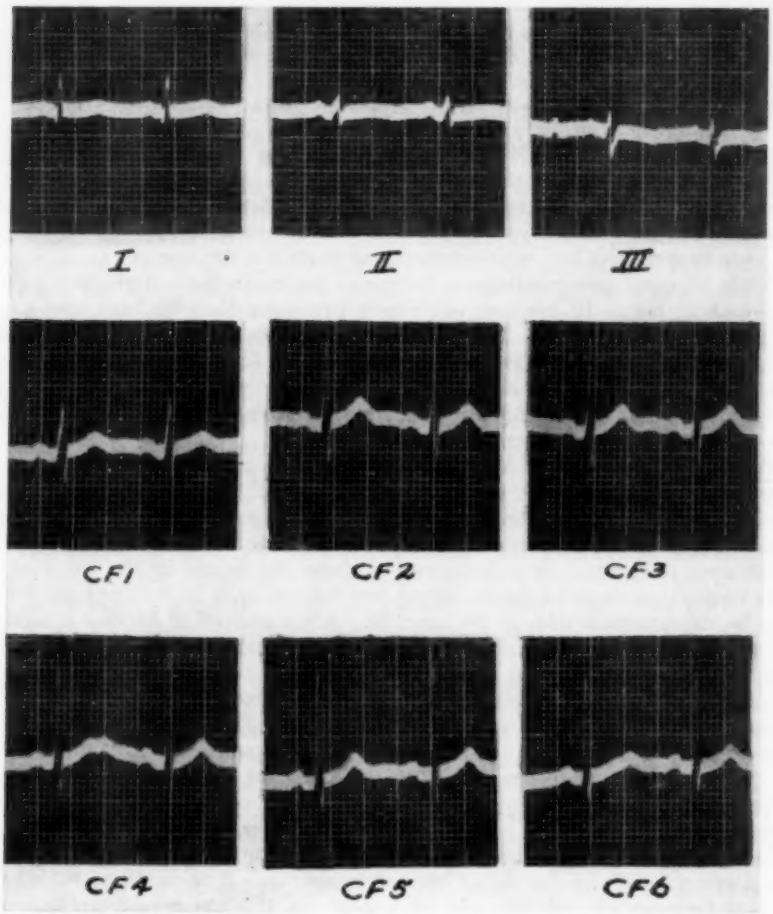

FIG. 5. A representative electrocardiogram taken from one of the "wet" cases.

in each group, showed values higher than 1.09, the upper limit of normal for men,[35] the three wet cases presenting ratios of 1.15, 1.16, and 1.10, and the three dry cases 1.11, 1.15 and 1.10, respectively.

The electrocardiographic tracings in the control subjects were all normal. Not shown in the wet and dry groups were several instances of slight elevation and abrupt take-off of T waves, with tall, pointed T. The ratios for the Q–T intervals were also slightly less in the control subjects, ranging between 0.96 and 1.10.

A typical electrocardiogram from one of the wet cases is shown in figure 5.

The Liver. Clinically there was no evident jaundice in any patient. Determinations of serum bilirubin were carried out according to the method of Malloy and Evelyn,[36] all patients showing less than 1.0 mg. per 100 c.c. of blood at intervals throughout the study. There was no essential difference between the wet and the dry groups.

Tests of thymol turbidity on blood serum by the method of Maclagan[37] were done at weekly intervals. Throughout the study all patients, as well as controls, showed readings higher than four units, the amount regarded as the upper limit of normal for Americans. At the beginning of the study the patients in the wet group ranged in values from five to 19 units, average 12.3, and in the dry group from five to 19 units, average 10.3. By the end of the study the values in both groups were still elevated, in the wet cases ranging from eight to 19 units, average 14.0, and in the dry group ranging from eight to 21 units, average 14.8. These high levels cannot be regarded as due to malnutrition, since the 24 normal Japanese controls showed values ranging from four to 16 units, average 10.

Bromsulfalein Liver Function Test. This test was performed three times on each patient, using 5.0 mg. of the dye per kilogram of body weight. Zero to 1.0 per cent of the dye retained in 45 minutes was considered to be normal. Sixteen of the patients, 10 in the wet and six in the dry group, showed more than 1.0 per cent of the dye retained. There was a tendency toward greater retention (higher readings) in the wet group, four cases showing readings as high as 6 and 8 per cent. In the dry group the range was from 2 to 4 per cent, with one patient showing a reading of 7.5 per cent. As the observations continued, only two in the wet group and one in the dry group showed significant improvement in this test.

Urine Bilirubin Excretion. Partly as a check against serum bilirubin studies, and partly from a desire for more experience with the Watson-Turner modification of the Harrison test for bilirubin excretion in the urine,[38] two series of tests were performed on each patient. Morning urine specimens for six successive days were examined on each patient during two different weeks. Six patients in the wet group gave positive reactions consistently, five of mild degree, one with readings of 2 and 3 plus. In the dry group, four patients gave sporadic readings of trace to 1 plus. Patient 9 in the wet group, who died with cirrhosis of the liver, had a persistently positive reaction of trace to 1 plus, with readings of 2 plus on two occasions.

TABLE V

Free HCl in Relation to Type of Anemia

	Free HCl		No Free HCl (After Histamine)	
	Wet	Dry	Wet	Dry
Macrocytic	4	5	4	3
Normocytic	1	1	3	3
Microcytic	0	0	0	0

Stomach and Intestines. Because of the presence of a macrocytic anemia in a significant number of cases in both groups, gastric analyses were done on all patients. If the fasting specimens did not contain free hydrochloric acid, 0.5 c.c. histamine was given subcutaneously. As shown in table 5, over half the cases with a macrocytic type of anemia had free HCl present in the gastric juice; the remainder did not. Most of the cases with a normocytic anemia had no free hydrochloric acid present even after the histamine stimulation. Tests were repeated in all cases showing no

free HCl with histamine, and only one, a dry case, showed seven units in the second test.

Three patients in the dry group presented enough symptoms of gastrointestinal disturbance to allow roentgenologic studies to be carried out. It was unfortunate that all could not have had such examinations made. During observation, patient 18 developed anorexia, epigastric burning and cramps with distention, chiefly at night, with tarry stools that were guaiac positive after iron had been stopped. Roentgenograms showed a normal stomach and duodenum. Patient 19 developed persistent sharp pain in the epigastrium and right upper quadrant, but both stomach and duodenum were normal fluoroscopically. A week later he developed a purulent right empyema, sterile on smear and culture, that probably was the cause.

The majority of the patients had diarrhea just prior to or at the time of hospitalization that subsided promptly without special treatment. In patient 21, however, a mucous diarrhea with occasional blood persisted. Proctoscopic examination showed only mucus with some reddening of the mucosa, without amebae, and stools were negative for pathogens on culture.

Kidneys. Two kidney function tests, using phenolsulfonphthalein, 1.0 mg. intravenously, were done on each patient, with collection of urine samples at the end of one and two hours. On the first test only three of the wet cases showed as much as 40 per cent excretion in an hour. In the second hour both groups were similar, 15 to 20 per cent excretion. One week later all patients in both groups showed values within normal limits, the wet cases showing nearly 50 per cent excretion of dye in one hour and a total of nearly 50 per cent in two hours. Only one patient in each group excreted over 70 per cent of the dye in two hours.

The Dyes. A Japanese ophthalmologist performed this test with Snellen charts. Four patients, two in each group, with vision less than normal had worn glasses for correction for from four to 18 years. Patient 14 had defective vision of the right eye following an injury. All other patients had essentially normal vision.

Autopsy Findings *

The five patients in the study group who died (9, 10, 12, 16 and 20) were examined at autopsy. Unfortunately the autopsy protocol was lost for patient 10, who died of disseminated tuberculosis, and this case is not included in the discussion. The remaining patients included two "wet" and two "dry" cases. In order to augment the pathologic data, an autopsy was done on six additional patients who died among the general hospital population. The ostensible cause of death of these patients was starvation, and the patients included five wet cases and one dry case. Three aspects of the pathologic data have been selected for discussion.

The first consideration of the pathologic data is the presence of a disease state that is of importance as a cause of death. One of the wet patients in the study group (case 9) had atrophic cirrhosis of the liver, the diagnosis of which had been considered but had not been established prior to death. The liver weighed 660 gm., its surface was nodular, it was firm in consistency, and it had a dull grayish brown color. The liver offered increased resistance on sectioning, the cut surface was nodular and dull brown in color, and its normal architecture was destroyed. The microscopic sections

* All autopsies were performed by Capt. Sam. D. Cummins, M. C., on the unembalmed cadavers, in most instances within one hour of death.

showed perilobular infiltration with macrophages and lymphocytes, marked fibroblastic proliferation and regeneration of bile ducts. A dry patient in the study group (case 16) had an extensive *Endamoeba histolytica* ulcerative colitis and acute fibrinous peritonitis. The patient had had severe abdominal pain and a bloody diarrhea and was prostrated, but the diagnosis had not been established because stool examinations for amebae had been negative and a proctoscopic examination had not been done. At autopsy the entire colon and rectum (but not the appendix) showed numerous ulcers with ragged, undermined borders, that penetrated to the serosa. The ulcers varied in size, the largest measuring 8 by 2 cm. The microscopic sections showed numerous trophozoites of *E. histolytica* in the submucosa and a few in the serosa. Although a grossly visible perforation of the colon was not demonstrated, the peritonitis was considered to be secondary to the amebic colitis. Among the six patients who died in the general hospital population and who were selected for postmortem examination, only two had a specific disease that was of importance as a cause of death. In both cases there were numerous deep ulcers involving the entire colon which measured up to 3 by 2 cm. The gross and microscopic appearance of the ulcer was typical of that caused by *Shigella*. There was, however, no bacteriologic confirmation in either case.

The second aspect of the pathologic data selected for consideration is the tissue changes due to starvation. The findings in the wet patients and the dry patients were similar. The *subcutaneous fat* in every case was described as being scant or absent. The *skeletal muscles* grossly were atrophic, flabby and pale brown in color, and the microscopic sections showed the fibers to be small and separated from the sarcolemma, with degeneration of the fibers in some instances. They stained poorly, and the striations were indistinct or absent. The nuclei were closely approximated. The *heart* in every case was atrophied, with an average weight of 164.5 gm. and a range of 140 to 200 gm. The muscle was easily compressible and pale brown in color. The valves were competent and normal and the coronary arteries patent and normal in every case except one, which showed an occasional, small (3 by 4 mm.) atheromatous plaque. The microscopic sections showed fragmentation of the myofibrils, with loss of striations and small nuclei in close approximation. Occasionally small focal infiltrations of round cells were present in the subepicardium and myocardium. The *liver* was atrophic and was similar in all the cases except the one (case 9) of atrophic cirrhosis described above. In the microscopic sections the hepatic cells were small and the cytoplasm stained poorly. The nuclei were in close approximation. In many cases there were small collections of round cells in the portal spaces. In one case, central necrosis of the lobules, with infiltration of round cells and polymorphonuclear neutrophils and regeneration of the liver cells, suggested a mild infectious hepatitis. The gall-bladder and common duct were normal in every case. The *pancreas* was atrophied in every instance and the lobules were small. In the microscopic sections

the acinous cells were shrunken and the cytoplasm was granular and stained poorly. The nuclei were small and in close approximation. Many of the acinous cells were vacuolated. The islets of Langerhans were small and stained poorly in many cases. Small collections of round cells were present in the connective tissue in many sections. The *kidneys* did not show striking changes due to starvation and were normal except in one case. This patient, a wet case, had evidence of nephrosclerosis and pyelonephritis, with thickened arteriolar walls and narrowed lumina with glomeruli in various stages of fibrosis. Collections of round cells around the glomeruli and infiltrations of round cells and polymorphonuclear neutrophils in the interstitial tissues and around the collecting tubules were present in this case. In the remaining cases the arterioles were normal while the glomeruli were smaller than normal in size. The collecting tubules frequently stained poorly, and occasionally the epithelial cells were vacuolated. There was very little round cell infiltration in the kidney sections. The *testes* did not show a uniform effect from starvation. Two cases showed no evidence of spermatogenesis, and another two cases showed but little spermatogenesis. There was some atrophy of the tubules but only a rare collection of round cells in the interstitial tissues. The *thyroid* gland was uniformly affected. The follicles were small, the epithelium was flattened, and colloid material was decreased or absent. In a few sections the connective tissue was increased and there were collections of round cells. The cortex of the *adrenal* glands was poorly stained, with a foamy or vacuolated appearance in every case. Similar changes were noted in the medulla in three cases. In the *pons* the ganglion cells uniformly were poorly stained, with granular cytoplasm and eccentric nuclei. The microscopic sections of the *myelinated nerves* showed varying degrees of degeneration and vacuolation of the myelin sheath and, in several cases, round cell infiltration of the epineurium. Microscopic sections of the *bone marrow* were reported in six cases, and were normal in four of them. Eosinophilia was present in two cases. One of the cases had ancylostomiasis and the other case had no intestinal parasites. Thus the bone marrow did not appear to be affected by starvation in this series of cases.

The third aspect of the pathologic data selected for discussion is some incidental findings. Edema was a striking clinical feature in the wet patients. It was present in the dependent subcutaneous tissues and in the loose areolar tissues of the omentum, mesentery, mediastinum and subepicardium, also occurring as free fluid in the peritoneal and pleural cavities. In the dry cases these tissues were dry. Edema was not present in the various organs of the wet or dry groups. Thus the weight of the brain in the seven wet cases ranged between 1,150 and 1,300 gm. with an average weight of 1,256 gm., as compared to a range in the three dry cases of 1,250 to 1,450 gm., with an average of 1,325 gm. The weight of the liver in the wet cases ranged between 525 and 1,000 gm., with an average weight of 765 gm., and in the dry cases the range was 750 to 1,050 gm., with an

average of 853 gm. The incidence of intestinal infestation was high. Seven of the 10 patients had a parasite at autopsy, five being infested with *Ascaris lumbricoides,* one with *Ascaris* and *Ancylostoma,* and one with *Ancylostoma.* Finally, the incidence of extensive dental caries was high, occurring in seven of the 10 patients.

Response to Treatment

The response to the treatment used was slow. During the first few days many patients ate only a small portion of the nutritious, but to them unpalatable, Army fare. This was improved considerably in the second week by having Japanese cooks prepare the food in their own way and by allowing the addition of some soy bean sauce. The latter, with its salt content, frequently caused edema to appear, if it was not present, or to reappear. Improvement was delayed further in 17 of the cases by attacks of malaria or episodes of diarrhea. Poor absorption of foodstuffs, likewise, is thought to have played an important rôle in delaying recovery, particularly in some of the more severe cases, as large masses of undigested food were found frequently in the feces on gross inspection.

In the wet group, six cases showed a moderate increase in strength, three a slight increase; in the remainder a definite progression of weakness culminated in death in two instances. Three cases lost none of their edema and six lost all of their edema, three of the latter with the help of mercurial diuretics. It was impossible to measure weight changes accurately in this group, but in general there was no apparent gain in weight.

In the dry group, four cases showed transient edema during the course of the study, usually in relation to a febrile episode due to malaria. As the malaria was brought under control, the edema subsided spontaneously and rather promptly. Two of the cases showed moderate increase in strength, eight showed none whatsoever, and two declined in vigor and eventually died. The weight could be measured more accurately in this group and only five showed a gain, which ranged from two to 11 pounds. Three showed no change at all, and four actually lost weight during the period of observation.

Improvement in the level of blood protein was almost negligible. There was a slight rise in albumin, globulin and total protein, yet the albumin fractions were still well below the so-called critical levels of 2.50 gm. per 100 c.c. for edema formation at the end of the study, when most of the patients were clinically edema-free.

Despite an adequate diet and daily administration of iron, there was very little rise in hemoglobin and red blood cell levels, at most about 1.0 gm. hemoglobin and 500,000 red blood cells in six weeks' time. If an erythrocyte sedimentation rate were to be used as any index of the patient's general condition, the progressive increase in this test during the study might suggest that at the end the patients were sicker than in the beginning. Such was not the case, however.

The most apparent improvement in the laboratory data occurred in the rise in blood cholesterol values in the dry group, which increased from an average low value of 79 mg. per 100 c.c. to a normal value for these Orientals of 125 mg. per 100 c.c.

The evidence from the serum thymol turbidity tests also would suggest that these patients were worse at the end of the study than at the beginning, but according to the bromsulfalein tests there was improvement.

At the end of six weeks the patients who survived were distinctly better. All were able to be up and about and were eating fairly well, and only a few showed significant edema on routine examination. Bladder and bowel function were becoming normal and bouts of diarrhea less frequent. The patients seemed to be gaining strength slowly.

Discussion

The special group of cases selected presented young and middle-aged males who had subsisted on a starvation diet of mostly vegetables and grasses for five to six months. During this period most of them had had bouts of malaria and diarrhea, had developed edema and had lost much weight. All were very weak. In their poor physical state the question that aroused our chief interest was the cause of the edema. Why should some of the cases have such massive accumulations of edema, and others none, with the majority of the other physical and laboratory findings so comparable in the two groups?

The first assumption was that we were dealing with beriberi, wet and dry. Our knowledge of beriberi consisted chiefly of the descriptions we had had from the studies of Keefer,[39] Weiss and Wilkins [40] and Blankenhorn.[41] Our patients did present edema and neurologic findings, but here the similarity stopped. Keefer mentioned serous effusions in beriberi to which our cases would conform. Weiss and Wilkins mentioned moderate lowering of serum proteins and moderate elevation of fasting blood sugar. In contrast, our cases had rather marked lowering of serum proteins, and normal to low fasting blood sugar levels. On neurologic examination the patients in this series showed rather minor sensory and few motor changes. These were not striking. In comparing these findings with those recorded during the war by Spillane,[42] we felt that our cases were not beriberi. They did not respond at all well to treatment, or develop chronic and severe neurologic manifestations, as Spillane points out for subacute and chronic beriberi. Furthermore, during the course of the study the Japanese doctors maintained that these were not cases of beriberi, but could not explain their reasons to our satisfaction. Finally, pathologic study failed to reveal the "hydropic degeneration" described by Keefer [39] and Weiss and Wilkins [40] for beriberi heart.

The presence of dyspnea, palpitation and pleural effusion, as well as peripheral edema, particularly in the wet group, next centered our attention

on the heart. The findings of a heart of normal size in all, normal or low blood pressure, no murmur or gallop rhythm, a normal venous pressure, whether in the wet or dry group, and no significant electrocardiographic change were to us good evidences against heart disease and heart failure as the cause of the edema. Digitalis was not administered to any patient, and yet many of them lost their edema while under observation. Pathologic study of the hearts did reveal some brown atrophy, fragmentation of myofibrils and loss of muscle striation.

Careful observations were carried out to detect a renal component in the picture. There was transient albuminuria and glycosuria, but in our further studies we were unable to establish clinically the presence of nephritis as the cause of the edema. Furthermore, microscopic examination of the kidneys showed no evidence of nephritis, except in one wet case (taken from outside the series) with pyelonephritis.

There was no evidence of venous or lymphatic obstruction as the cause of the edema.

We had no way of estimating the probable sodium intake of these prisoners prior to capture. There may also have been differences in sodium clearance in the two groups. The effect of sodium on edema formation became strikingly apparent in some of the cases upon the addition of salty soy bean sauce to the diet to encourage food intake. Even so, all patients did not develop edema on soy sauce and, in some, edema receded with its continued use. Studies of sodium clearance might yield valuable information in future investigations of this sort.

An association between edema formation and the presence of an attack of malaria [40] or diarrhea became very obvious, but an increase in edema after the institution of a normal diet, as mentioned by Stapleton,[21] was not apparent in these Japanese prisoners. The edema responded quite well to mercurial diuretics in the few instances in which they were used.

What then might explain the clinical picture which we encountered? The wet cases in our series appeared to fall into group 2 of famine edema, described by Beattie, Herbert and Bell [30] under the term "hypoproteinemic famine edema." (Group 1 is "isohydric famine edema," in which total plasma proteins and the albumin fraction are normal.) Presumably such cases may have an increased capillary permeability with the escape of protein into the extracellular fluid compartment. This still does not explain the lack of edema with the same total protein and albumin levels in the dry group. Interestingly, Beattie et al. found hydrothorax and hydroperitoneum for a brief period in only one of 11 patients with hypoproteinemic edema, whereas all of our wet cases except two had hydrothorax of mild to marked degree, with ascites present in 11. We likewise observed a delayed diuresis, slow disappearance of edema and, frequently, weight loss under treatment, as did Beattie, Herbert and Bell.

Our cases also are comparable in some respects to the volunteers studied by Keys [27] and Henschel [28] and their associates, with four major differences.

None of our cases showed (1) profound bradycardia, (2) a notable fall in plasma protein concentration, (3) a venous pressure of 50 per cent below normal; and (4) pleural and peritoneal effusion was present (in the wet group). In none of Henschel's 32 cases was there ever ascites or hydrothorax. In fact, this author states that "this again is similar to natural famine edema where accumulations of fluid in the body cavities is not common except in the presence of other complications." In our series of Japanese prisoners we found no "complications" to explain the serous effusions in the wet group.

From their studies, Keys and Henschel concluded that the edema of simple caloric starvation is a manifestation of a state of dynamic nonequilibrium of the capillary wall, reflecting largely a reduction in cellular mass without a large change in the absolute amount of extracellular fluid. Youmans [22] would place such simple caloric starvation almost entirely on a protein deficiency basis.

The evidence in our series of cases seems to suggest five factors in the causation of the clinical picture: (1) inadequate food intake, probably largely in protein; (2) changes in the bowel, along with infection and worms, causing diarrhea (? sprue) with resulting lack of proper absorption and assimilation of food; (3) consequent lowering of plasma total proteins and its effect on colloid osmotic pressure; (4) anemia, frequently macrocytic, and (5) some element of vitamin deficiency, probably B and possibly C, to account for the neurologic changes and the altered capillary permeability mentioned by Keys and Henschel.

The lack of adequate food intake was evident. But the majority of the facts seemed to point to disturbances in the gastrointestinal tract as second in importance to lack of food intake as the cause of the clinical picture.

The relatively large number of cases with achlorhydria was of interest. That all of them had intestinal parasites may have added to the picture. The lack of proper absorption of foodstuffs was manifest in many ways. Even to the end of the study, some patients were still passing rather large quantities of undigested food particles by rectum. The flat glucose tolerance tests, the macrocytic anemia (? deficient absorption of extrinsic factor), the failure to improve the hematologic picture significantly with diet and iron (? lack of protein or iron absorption, or both), the very slow rise of plasma protein values, the ineffectiveness of oral atabrine to counteract malaria in some cases, and, finally, the failure of the majority to gain weight were to us evidences of faulty absorption in the intestinal tract. Yet that was not true apparently for all substances, for the subsequent return to normal of low cholesterol values in the dry group can be explained best on the basis of lack of intake, followed by adequate absorption after an adequate diet was supplied. As these evidences became apparent, it was most unfortunate that roentgenographic studies of the small bowel could not be carried out, since they might have been enlightening.

Of additional interest were the disturbances of liver function by several tests, the normal or even elevated basal metabolic rates despite malnutrition, and the rather marked creatinuria associated with the muscle wasting.

Our cases appear to fit best into a category of *chronic malnutrition with diarrhea*, with or without nutritional neuropathy, as described by Spillane.[42] He cites the effectiveness of nicotinic acid in controlling such diarrhea. We had no nicotinic acid to administer, but the diarrhea often subsided spontaneously within a few days. Although our study lacked roentgen surveys of the small bowel, in Spillane's series of such cases in German and British patients radiologic examinations by the method of Golden [43] showed no sigficant abnormality.

A number of the findings hinted at sprue. Although all of the patients did not have all of the features, the presence of glossitis, macrocytic anemia and diarrhea with undigested food particles was suggestive. There was no excess of fat in the stools. Liver extract or folic acid was not available for therapeutic trial.

The clinical picture in this group of Japanese prisoners appears to have been one of nutritional hypoproteinemia with a spruelike syndrome. We have no adequate explanation for the fact that some presented massive edema and others did not.

Summary and Conclusions

From among thousands of Japanese prisoners of war at the 174th Station Hospital, New Bilibid Prison, Muntinlupa, Luzon, Philippine Islands, 24 of the most starved patients were selected for special study. They were divided into two groups, 12 with massive edema and 12 with no edema. Detailed clinical and laboratory studies were carried out over a period of six weeks for comparison of the two groups. Twenty-four apparently healthy Japanese ward helpers were used as controls.

All of the cases showed loss of weight, wasting, diarrhea, dyspnea and palpitation on exertion, and a few showed limited neurologic symptoms. All had anemia, intestinal parasites, hypoproteinemia, abnormal liver function tests and evidences of improper intestinal absorption. All of the "wet" cases had hydrothorax and ascites, whereas their absence was striking in the "dry" group.

Many other studies, including blood hematocrit, specific gravity, sedimentation rate, urinalyses, stool examinations, blood chloride levels, glucose tolerance tests, basal metabolic rates, urinary creatine, studies of the heart and circulation, viz., circulation time, venous pressure, electrocardiograms, liver studies, such as thymol turbidity and bromsulfalein tests, bilirubin excretion, and renal function tests, failed to elucidate significant differences between the "wet" and "dry" cases. The only essential difference in the two groups, and one which we are unable to explain, was a consistently lowered blood cholesterol in the dry group, which returned rather promptly to normal under dietary treatment.

Despite good medical care and a high calorie, high vitamin diet, including yeast and vitamin supplements, the response of these patients to treatment was slow.

During the course of the study five of the group of 24 cases died and were autopsied. Six additional cases from outside this special group who died from malnutrition alone also were autopsied, to augment the necropsy material for study. The atrophic changes in tissue, cellular infiltrations, etc. were the same in the two groups, the only difference being the presence or absence of edema.

From this study we have drawn the following conclusions:

1. An analysis of the findings does not support our early assumption that these were cases of wet and dry beriberi.

2. There was no evidence clinically or pathologically of beriberi heart disease or other organic heart disease, nephritis, or venous or lymphatic obstruction to account for the edema.

3. A number of the patients, both wet and dry, exhibited increasing edema with an intercurrent attack of malaria. On the other hand, control of the malarial attack was frequently associated with diuresis and loss of edema fluid. The reasons for this were not apparent.

4. The clinical picture was one of nutritional hypoproteinemia, with a spruelike syndrome manifested by marked alterations of serum proteins, with or without edema, with glossitis, diarrhea and marked wasting. These changes were attributed to inadequate food intake, probably with secondary alterations in the gastrointestinal tract which prevented the proper absorption and assimilation of foodstuffs.

5. With nearly all of the abnormal findings so similar in the two groups, we are unable to explain why some should have had such massive edema and the others none. Possibly differences in sodium intake prior to capture, or in sodium clearance, may suggest an answer.

We wish to acknowledge the full coöperation of the following military personnel, without whose help the study could not have been carried out: Capt. Arthur L. Ruby, M. C., who spent full time in this study, 174th Station Hospital; Col. Dwight M. Kuhns, M. C., Commanding Officer, 19th Medical General Laboratory; Capt. Robert M. Melampy, Sn. C.; Capt. Samuel D. Cummins, M. C.; Capt. Aubrey B. Harwell, M. C.; Lt. C. Calmon, Sn. C.; all of the 19th Medical General Laboratory; Capt. Homer H. Hunt, M. C., 174th Station Hospital Laboratory; Lt. Alexander Shoob, M. A. C., 4th Medical Museum, and the enlisted personnel of the two laboratories.

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PULMONARY MONILIASIS *

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The concept of pulmonary infection by certain mycotic organisms has gained recognition in recent years with proof that some of these agents are pathogenic. Perhaps the best example of such an infection is coccidioidomycosis. In addition to the established pathogens, there are other agents, including *Candida albicans,* which we believe are pathogenic also.

The problems in the diagnosis and treatment of *C. albicans* infections are manifold, and their solutions often obscure. It is the purpose of this paper to emphasize and clarify some of these problems by a review of the subject and by the presentation of six illustrative cases, one with autopsy findings.

Historic

Castellani,[1] while working in Ceylon in 1905, noted a patient with a Monilia infection of the lung. In the following year, he was consulted by a tea taster who, because of a chronic cough, had been diagnosed as having pulmonary tuberculosis. This patient described his ailment as "tea taster's cough," and stated that he had developed the symptoms after inhaling, as well as tasting, crushed tea leaves. Numerous mycelial filaments and yeastlike bodies, but no acid-fast organisms, were isolated from his sputum. Castellani insufflated the respiratory tract of a guinea pig with the cultured material, which had been identified as a Monilia. Subsequently, the animal died of bronchopneumonia. Later Castellani studied the organisms and found that biochemically identical strains varied enormously in their virulence.

In 1915, Boggs and Pincoffs [2] described the first case of pulmonary moniliasis in the United States. Since that time, numerous instances of the disease have been reported from various parts of the world.

More recently, attention has been focused on another respiratory disease which is related to a definite occupation and is appropriately called "thresher's lung." [3, 4] While the etiology has not been established clearly, it would appear that the disease is mycotic in origin, and that in certain instances *C. albicans* may be the responsible agent. In some of these cases, the disease is similar clinically to sarcoidosis. Tornell [3, 5] has asked whether sarcoidosis

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might be a variant of a fungous infection. One of our cases (case 6) illustrates the difficulty of clear differentiation between moniliasis and sarcoidosis.

Clinical

Although pulmonary moniliasis is found in all climates and among all racial, age and sex groups, its exact incidence is unknown. Published reports on bronchomycosis, or coexisting tuberculosis and bronchomycosis, give some idea of the relative importance of these infections.[6, 7, 8, 9, 10] Reeves [6] noted that Monilia was the agent in 40 of 79 cases of bronchomycosis. Of these 40 cases, 21 patients were male and 19 female. The duration of symptoms was from one month to five years and, in one case, 15 years. Greer and Gemoets [7] and Greer [8] reported the isolation of fungi from the sputum expectorated by 45 of 310 consecutive patients admitted to the Houston Tuberculosis Hospital. They stated, however, that in only 18 of the 45 patients were fungi found in specimens obtained by intratracheal aspiration. The organisms isolated from each of the 18 were pathogenic when inoculated into animals. In one patient *C. albicans* was found in both the expectorated and the aspirated sputum.

Many authors [11, 12, 13, 14, 15, 16, 17, 18, 19] have given adequate clinical descriptions of primary Candida infections of the lower respiratory tract. In general, three clinical types are recognized: mild, intermediate and severe. In the mild type, there is cough with a mucopurulent sputum. Results of a physical examination of the chest are negative, although occasionally a few scattered râles are heard. A frequent diagnosis of this form of the infection is chronic bronchitis. In the intermediate type, there is low-grade fever, some bronchial hypersecretion and moderately severe cough. Dyspnea may be present. Physical findings are midway between those of the mild and of the severe types. Frequent diagnoses made in these cases are chronic bronchitis, bronchial asthma and bronchiectasis. The severe type of the disease, when acute, may resemble lobar or bronchopneumonia; when chronic, it may mimic pulmonary tuberculosis. Fever, weight loss, night sweats, cough, dyspnea, chest pain, anemia and emaciation often are present. Hemoptysis is frequently found. On physical examination, there are signs of pleural thickening and patchy consolidation in the lungs. Healing, with a high degree of fibrosis, may lead to chronic dyspnea and cough and, eventually, to cor pulmonale.

Steinfeld [20] suggested that in "cigarette cough," one must rule out mycotic infections. In many of the reported cases of pulmonary moniliasis, the patients complained of attacks of bronchial asthma. Craik [21] described a patient with asthma and bronchitis. Monilia were present in the sputum, but no acid-fast organisms were isolated. Under therapy with alkalies, iodides and adrenalin, the patient remained in good health. In 1924, Steinfeld [22] noted a series of individuals suffering from bronchial asthma in whose sputum Monilia were present. Treatment with iodides and in-

jections of killed cultures of Monilia produced beneficial results. Galbreath and Weiss [23] reported on a patient who showed clinical symptoms of pulmonary tuberculosis, but in whose sputum *Monilia pinyoni* (ashfordi) were seen consistently and acid-fast organisms were absent.

Diagnosis

The disease is diagnosed by the clinical manifestations mentioned previously, together with certain radiologic evidence, the consistent finding of large numbers of *C. albicans* in carefully collected sputum specimens and the absence of *M. tuberculosis* in the sputum. The mere presence of *C. albicans* is not indicative of disease. The organisms are seen frequently in normal sputum, urine and feces, and may be found in association with almost any pulmonary disease.[18, 19]

The roentgenographic appearance of the lungs is important in establishing a clinical diagnosis. In brief, the findings generally are those of extensive hilar and peribronchial thickenings, with lesions which usually are of larger size than those found in miliary tuberculosis (although they may be miliary in appearance) occurring in scattered patchy foci or in local or widespread consolidations; the number of lobes involved is variable. The lesions are labile, and serial thoracic roentgenograms show the fluctuant nature of the infection. There may be cavitation resembling that seen in bronchiectasis. Extensive fibrosis with widespread infiltration throughout the lungs appears to be a common result of the disease.[18, 24, 25, 26] Doub [27] suggested that mycotic infections can be precursors of miliary pulmonary nodules.

Marett [28] and Fawcitt [29] have explained the appearance of the lungs in roentgen films as follows: In culture, Candida grow in tubes either in collars or on the surface in a sheet, or they may start as isolated colonies which spread into a confluent sheet. A similar sheet is said to form by the spread of colonies over the surface of the bronchial epithelium, with resultant ulceration, erosion and dilatation which give the roentgenologic appearance of bronchiectasis. The collar-type of colony may occlude the bronchiole, producing a collapse of the distal alveolus which results in a patchy, fluffy or coalescent appearance.

The laboratory criteria are summarized in detail elsewhere [18, 19] but may be restated briefly. The erythrocyte sedimentation rate is usually elevated in an active infection. A normal white blood cell count is commonly found, although there may be a leukocytosis. Skin tests, agglutination tests,[30] complement fixation tests and precipitin tests for *C. albicans* have been described but are not dependable for accurate diagnosis. Skin tests may be negative in the presence of a severe infection.

Mycologic Diagnosis

Since the term Monilia is not taxonomically correct, it has been discarded by medical mycologists, who generally agree that the generic designation

Candida should be adopted. The classification of the "Monilias" isolated from man has presented many difficulties. In many instances, investigators are not in agreement as to the number of species which should be included in this group of yeastlike organisms. Methods of classification employed in the past have given rise to a large number of confusing specific and generic names. More recently, a concerted effort has been made by some authorities to standardize and improve the procedures used in classification, so that at present the genus Candida contains comparatively few valid species. *C. albicans* is the one member of the genus commonly associated with disease processes in man; it is the only one which is pathogenic for laboratory animals.

Among the various "systems" for the identification of species of Candida are those which have been proposed by Castellani,[31] Dodge,[32] Stovall and Bubolz,[33, 34] Martin and associates,[35] and Langeron and Guerra.[36] Skinner, Emmons and Tsuchiya,[37] recognizing the difficulties inherent in such "systems," have suggested still another classification of Candida species, utilizing criteria employed by Martin and his associates [35] and by Langeron and Guerra.[36] The Mycology Laboratory at the University of California Medical School is presently following the methods developed by Martin and associates [35] for the differential diagnosis of species of Candida.

Treatment

Treatment has been found uniformly difficult and unsatisfactory. The medications mentioned most prominently in all articles are the iodides. Potassium iodide orally, sodium iodide intravenously, ethyl iodide by inhalation,[38] and iodized poppy seed oil intratracheally [39] have been used. Proof of the absence of infections with *M. tuberculosis* prior to the use of iodides is of great importance (case 1).[40, 41, 42] Conant et al.[18] stressed the fact that before iodides are given, the patient should be skin-tested with *C. albicans* vaccine and, if hypersensitive, should be desensitized.

Diverse vaccines and antisera have been used with variable success (cases 3, 6).[43, 44, 45] Thymol has been recommended, but Stovall, Pessin and Almon [46] report that large doses of thymol by mouth give no protection against the intravenous injection of virulent Monilia in laboratory animals. Intravenous gentian violet, balsamics, arsenic, glycerophosphates, quinine and other medications have been tried without remarkable success. Merthiolate has been used successfully against *C. albicans* in vitro but has not yet had a reported clinical trial.

Case Reports

In recent years a number of patients studied at the University of California Hospital have shown clinical, roentgenographic and laboratory features suggesting pulmonary moniliasis. The records of six patients with characteristic clinical findings are reported here in detail.

Case 1. A 22 year old white female was in excellent health until two years before her entry into the hospital. In 1929, she developed clinical and roentgenographic evidence of tuberculosis and was admitted to a sanatorium, where she remained for one year. After showing improvement, she suffered a relapse late in that year. Pneumothorax was attempted twice without beneficial results. The patient was then admitted on April 28, 1931, to the Medical Service at the University of California Hospital.

Physical examination revealed a wasting of the chest on the left anterior side and signs of cavitation. On the right side of the chest, fine râles were heard over the apex. P_2 was greater than A_2. The edge of the spleen was palpable, rounded and tender. The liver was felt about 2 cm. below the right costal margin. There was marked clubbing of the fingers and toes. Roentgenographic examination of the chest showed the mediastinal contents shifted to the left. An irregular shadow, with its greatest density near the left hilus, extended to and occupied the area at the base. One small rounded area, suggesting a small cavity, was seen at the level of the third left anterior interspace. A second film one month later showed 50 to 100 small cavities, varying from a few millimeters to a centimeter or more in diameter, in the left upper lobe.

Laboratory examination revealed an anemia (hemoglobin 50 per cent) and a moderate leukocytosis with a normal differential distribution. The urine was normal. The sputum was thin and fetid, with a foul, fermented ("brewery") odor. Sputum examination at three different times showed large numbers of small budding yeastlike organisms which were identified subsequently as *C. albicans.* Repeated sputum specimens were reported as negative for acid-fast bacilli. A tuberculin skin test was positive; coccidioidin skin tests and serologic tests for syphilis were negative.

The patient was treated with potassium iodide, intravenous sodium iodide and general supportive measures. Following treatment, *C. albicans* could not be cultured from her sputum. Throughout the course of her illness, the volume of sputum remained constantly at about 250 c.c. per day. Following iodide therapy, the sputum became odorless. The patient's temperature ranged daily from 37° to 39° C. until the last four days of her hospital stay when, well saturated with iodides, she became afebrile.

A month and a half after she entered the hospital, the patient developed auditory hallucinations which were thought to be toxic in origin. She was transferred to the psychopathic ward at the San Francisco City and County Hospital, and from there to Agnews State Hospital in August, 1931.

The first sputum specimen taken at the latter institution was negative for *M. tuberculosis,* but the next two were positive. The patient died in September, 1931, presumably of pulmonary tuberculosis. No autopsy was performed.

Comment: The illness of this patient illustrates a case of pulmonary tuberculosis with either a secondary pulmonary moniliasis or a primary moniliasis in the presence of arrested tuberculosis. There is also the possibility that the pulmonary tuberculosis was secondary to an initial moniliasis. Death may have been the result of the breakdown of arrested lesions and the dissemination of tuberculosis through the activity of the iodides.[42] The absence of acid-fast organisms before iodide therapy and the disappearance of *C. albicans* with therapy, together with the subsequent reappearance of *M. tuberculosis,* suggest that the last explanation may be correct. The presence of active tuberculosis before and after treatment makes it difficult to accept this case solely on the basis of primary pulmonary moniliasis. The

fatal termination emphasizes the dangers of using iodides in patients known to have had recent active tuberculosis.

Case 2. A 38 year old white male entered another hospital in May, 1935, after drinking lye, and was discharged as recovered two weeks later. Shortly thereafter he began to have a temperature ranging from 99° to 103.5° F. During July, 1935, he started to have severe chills which usually developed in the morning, lasted about 30 minutes, and were followed by diaphoresis. He developed an unproductive cough.

The patient entered the University of California Hospital on the Medical Service on July 22, 1935. Physical examination at this time revealed petechiae and a papular eruption over the middle third of the anterior aspect of the right leg. The posterior pharyngeal wall was reddened and granular. The patient's chest expansion was poor; he had shallow respirations and was dyspneic. There were constant rough irregular moist râles, especially over the larger bronchi. A definite mass, thought to be spleen, was felt in the left flank beneath the costal margin. There were cyanosis of the beds of the nails and early clubbing of the fingers.

On laboratory examination, the stool, urine, blood, serologic tests for syphilis, and agglutination tests (for typhoid, paratyphoid A and B, tularemia and brucellosis) were negative. Monilia were cultured from two successive sputum specimens, each of which was negative for acid-fast bacilli and other pathogenic organisms. Thoracic roentgenograms showed the left lower lobe completely consolidated and the lower portion of the left upper lobe partially consolidated. The lower portion of the right upper lobe and the entire middle lobe were consolidated. There was thickening of the interlobar fissure between the right middle and right upper lobes; a small pleural effusion was present at that level.

The patient, who was critically ill when he entered the hospital, was treated intensively with supportive measures and improved remarkably. His temperature returned to normal.

A sputum specimen cultured in August, 1935, was found to contain *C. albicans.* These organisms were inoculated intravenously into a rabbit at the rate of 0.5 million cells per 100 gm. of body weight. The animal died four days later. Multiple lesions characteristic of moniliasis were found on postmortem examination. Histologic sections of the kidneys, spleen and lungs showed extensive production of mycelia within the tissues.

When the patient was dismissed from the hospital in mid-August, potassium iodide was added to his regimen. Because of a feeling of well-being, despite moderate dyspnea, he voluntarily discontinued the potassium iodide after one month. Shortly thereafter, in October, 1935, he reëntered the hospital with malaise, a temperature of 40° C., chills, generalized aches and pains, and a cough productive of frothy sputum, all of several days' duration. On examination, coarse râles and moderate dullness were found over the midportion of both lung fields. Several hours after hospitalization, his temperature returned to normal. The patient was discharged in two days without having received specific therapy.

Thereafter, the patient took thymol daily. There was pronounced symptomatic improvement of cough and fatigue. He gained weight, although moderate exertional dyspnea remained. Sputum and urine specimens were negative for *C. albicans* in February, 1936.

From August until December, 1936, the patient took no medication. During November he developed a cough productive of small amounts of white frothy sputum and suffered from intermittent attacks of generalized aching. In December his sputum was found to contain *C. albicans.* Culture of a urine specimen was negative. Thymol was given, and symptomatic improvement again was noted.

The patient did not return to the clinic until December, 1937, at which time he said that he had taken thymol until February, 1937, and then had discontinued all medication. Slight dyspnea had been present during the year. About once each month he had experienced episodes of malaise and weakness lasting for several days, during which he had a cough productive of a small amount of frothy sputum; in the interim he felt well. Except for a slight dullness and a few moist râles in the mid-portion of each lung field, the examination in December was negative.

Repeated roentgenograms of the chest at intervals from October, 1935, until December, 1937, were interpreted as showing no change from those made in July, 1935.

The patient has not been seen since December, 1937.

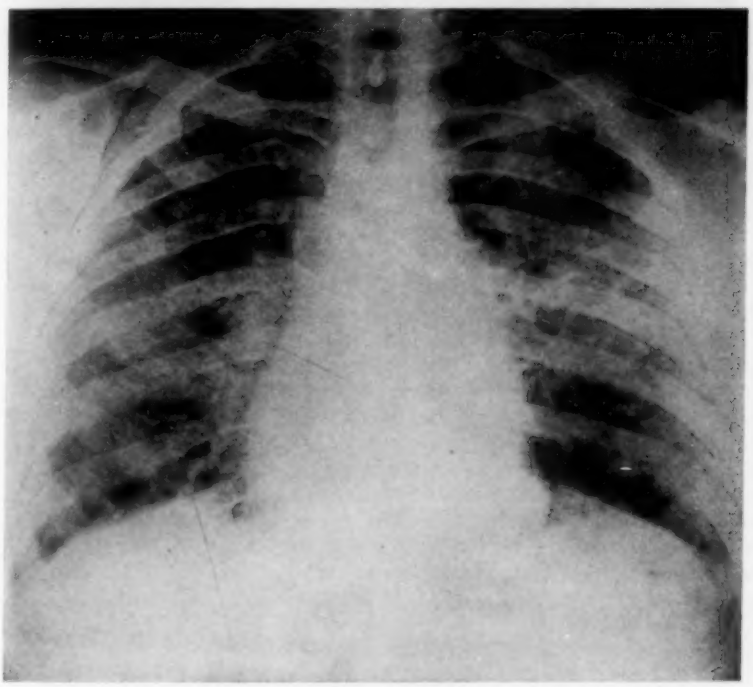

FIG. 1 *A*. Chest roentgenogram of June 9, 1936, shows the changes described in the text. Note the involvement of the basal lung field as compared with the apices.

Comment: This case demonstrates the diagnostic criteria described earlier in this paper. The patient's sputum consistently showed large numbers of *C. albicans* and an absence of *M. tuberculosis*. There were definite clinical features of the severe type of infection, with roentgenographic evidence of widespread consolidation of the lung. Finally, the patient showed improvement when he received iodides and thymol as specific therapy, and regressions when he did not. Whether the infection was primary or secondary is of little consequence, although it is highly probable that it was secondary to the ingestion of the lye. The important considerations were the recognition of the condition and the prompt response to therapy. In retro-

spect, it is of interest to note that each time the patient discontinued medication, he developed an exacerbation of his symptoms. The clinical diagnosis was "moderately severe pulmonary moniliasis."

Case 3. A 25 year old white male chiropodist had been well until the age of 13 years, when he began to have intermittent attacks of chills and fever, lasting several days, which were associated with vague aches and pains in the shoulders and arms. There was a cough productive of small amounts of sputum, accompanied by moderate dyspnea. Tuberculin skin tests were negative. The symptoms persisted for about a year, after which they disappeared.

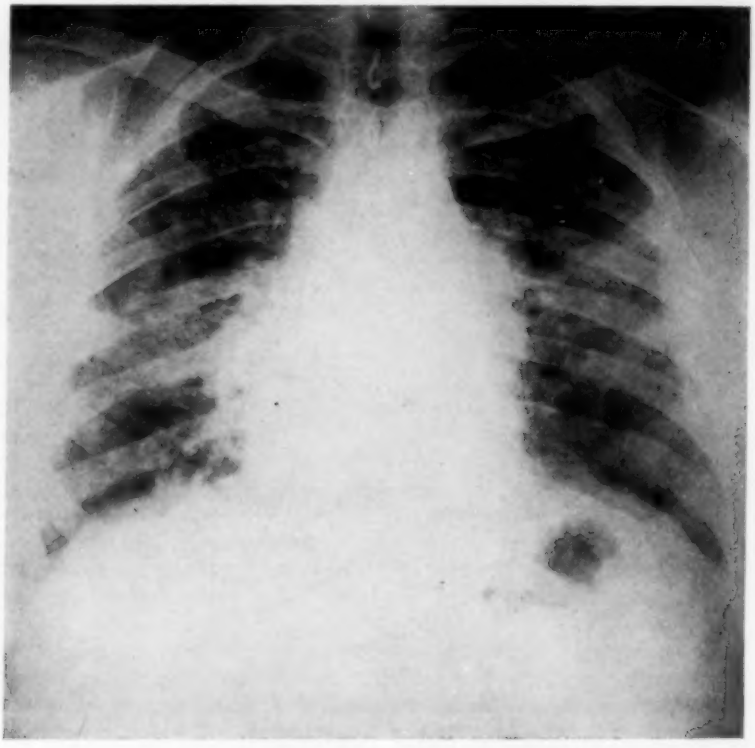

FIG. 1 *B*. Chest roentgenogram of December 10, 1936. Note the slight improvement as compared with the film of June 9.

In 1927, when the patient was 16 years old, roentgenograms of the chest revealed bilaterally enlarged hilar lymph nodes and increased markings in the right lung fields. At the age of 18 years his symptoms recurred and, together with a subfebrile temperature and night sweats, persisted as indefinite episodes until his entry in the hospital. Repeated sputum tests were negative for acid-fast organisms. Between the ages of 23 and 25, the patient noticed a feeling of constriction of the chest. During this period he lost about 20 pounds of weight.

Nine months before entry into the hospital, a roentgenogram of his chest was interpreted as showing metastatic malignancy. Several courses of deep roentgen-ray therapy were administered to the chest area, and some improvement was noted in thoracic roentgenograms.

At the time of hospital entry, on March 25, 1936, the abnormal physical findings were limited to the lungs. There was diminished resonance at the right apex posteriorly and over the second and third ribs anteriorly on the left. There were inspiratory squeaks throughout the left anterior and posterior lung fields.

On laboratory examination, urine, stool, red blood cell count and hemoglobin were normal. There were 3,870 white blood cells per cubic millimeter with a normal differential count. Roentgenographic examination of the chest (figure 1 *A*) showed a diffuse mottling throughout both lung fields, which was thought to be caused by the increased density of peribronchial tissues. There was a cavity in the upper right lobe at the level of the second costal cartilage at a depth of about 5 cm. There were other areas in both lungs suggestive of small cavities. The apices were less involved than other portions of the lung; the most affected areas were those directly lateral to the lung roots. Subsequent examination in October and December, 1936, showed slight regression of the lesions but no other changes (figure 1 *B*).

No specific therapy was administered. Spontaneous symptomatic improvement occurred after dismissal from the hospital. Sputum specimens examined two months later revealed large numbers of *C. albicans;* no acid-fast organisms were seen. A rabbit inoculated intravenously with 6.6 million organisms per 100 gm. of body weight died in nine days. Postmortem examination showed typical lesions in the kidneys, spleen, heart, brain, mesenteries and diaphragm. The lungs were severely hemorrhagic. *C. albicans* were recovered from the bile.

An autogenous vaccine prepared from the organisms isolated from the patient was administered three times weekly. The patient was also given thymol but, because of a gastric upset, this medication was discontinued. Tartar emetic and sodium iodide were administered intravenously for one month.

Two months following the first isolation of *C. albicans,* cultures of blood, sputum and urine were negative for the organisms. A sputum smear was negative for acid-fast bacilli. A single stool specimen was positive for *C. albicans.* One month later the sputum revealed the organisms, but urine specimens examined at the same time were negative. Sputum specimens were negative for *C. albicans* six months later (December, 1936), but were positive in March and May, 1937. A precipitin test was negative in March, 1937. During 1937 the patient took thymol and potassium iodide intermittently and had intervals of well-being, alternating with periods of exacerbated cough, increased production of sputum, moderate dyspnea and fever. During the overall course of his illness, the patient failed to show any consistent general improvement.

An appendectomy was performed late in May, 1937. A few days after surgery, the patient developed marked dyspnea and cyanosis and died shortly thereafter.

Postmortem Examination: An autopsy was performed by his local physician, and the specimens were sent to the late Dr. C. L. Connor at the University of California Hospital. Dr. Connor's pathologic report follows. (All specimens were received fixed in formalin.)

"*Macroscopic: Heart.* The pericardial cavity is smooth and essentially negative. The heart weighs 425 grams. It contains several opaque spots on the epicardium, but is otherwise normal on the surface. The myocardium is firm and contains no scars. The valves are negative; no measurements can be taken because of the formalin fixation. The left ventricle wall is about 1.6 centimeters in thickness. The right is markedly thickened and enlarged, showing a preponderant hypertrophy. *Lungs.* The lungs together weigh 1525 grams. They are voluminous and have not collapsed. On the surfaces of each there are fragments of comparatively old adhesions, and some new exudate mottled here and there. Parts of both lungs contain air, but are for the most part solid and gummy in consistency. On section, there are alternating patches of alveolar emphysema and atelectasis, with completely consolidated patches through-

out, mostly in the periphery, where a chronic, fibrosing lesion appears to be present. There is some possible thickening of the bronchial nodes on some of the sections, which becomes more evident near the hilus. Here, there is a definite chronic thickening of the bronchi. A pair of bronchial lymph nodes are definitely enlarged and contain whitish fibrous patches which may be exudate. Both lungs are essentially similar in character. *Spleen.* The spleen weighs 300 grams. There are numerous whitish patches beneath its capsule. On section, these resemble greatly enlarged splenic follicles, measuring up to 5 millimeters in diameter. The spleen is pulpy, but except for the whitish areas, is not remarkable. *Liver and Pancreas.* Sections of

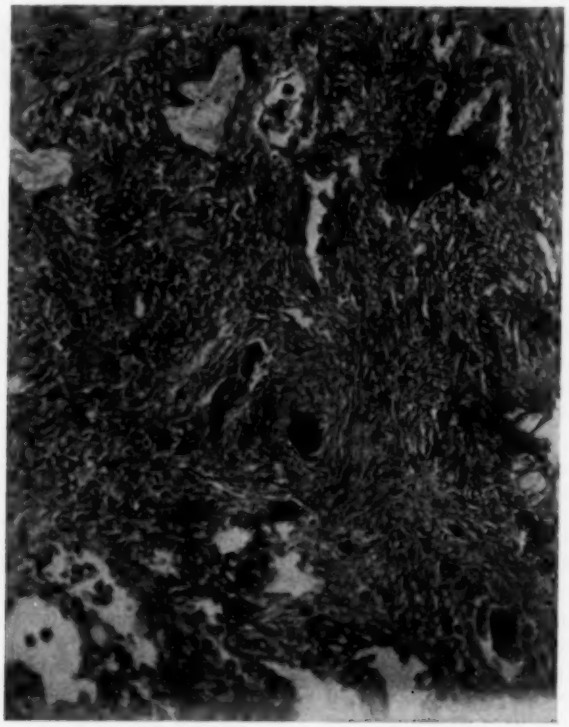

FIG. 2*A*. Section of lung (× 100) shows destruction of the parenchyma with replacement by fibrous tissue. Numerous multinucleated giant cells are present. Note the resemblance to the lesions of sarcoidosis.

these organs show no gross change from the normal. *Kidney.* A kidney, presumably the right, contains several deep scars from localized lesions. The scars have the conical shape of infarcts which are now healed. *Lymph Node.* A separate flat lymph node, origin unknown, contains a fibrosing lardaceous lesion.

"Microscopic: Heart. The muscle shows no particular change from the normal. Both endocardium and epicardium are negative. *Lungs.* Numerous sections show a widespread inflammatory process of an interstitial type in most places (figure 2*A,B*). The walls of the bronchi and bronchioles are thickened by a fibrous tissue proliferation. There are numerous lymphocytes scattered in the fibroblastic areas. Characteristic lesions are spotted along bronchi and at several points throughout the parenchyma. These form small tubercle-like lesions, and most of them contain one or more usually very large multinucleated giant cells. The pleura is thickened in

many places, with younger, still proliferating fibrous tissue. The tubercles mentioned contain some epithelioid cells, but lack the caseation and the lymphoid proliferation typical of tuberculosis. Likewise, the giant cells are usually larger and contain many more nuclei than the characteristic tuberculous giant cells. In none of the hematoxylin and eosin stained sections can definite organisms be seen. Acid-fast stains are negative, and most gram stains reveal nothing. A few gram-stained organisms are present, however, which are found to be about the size of a lymphocyte, with a capsular material which takes a fuchsin counterstain. These vary somewhat in size, and after a long search, a few can be found which are budding. In a few

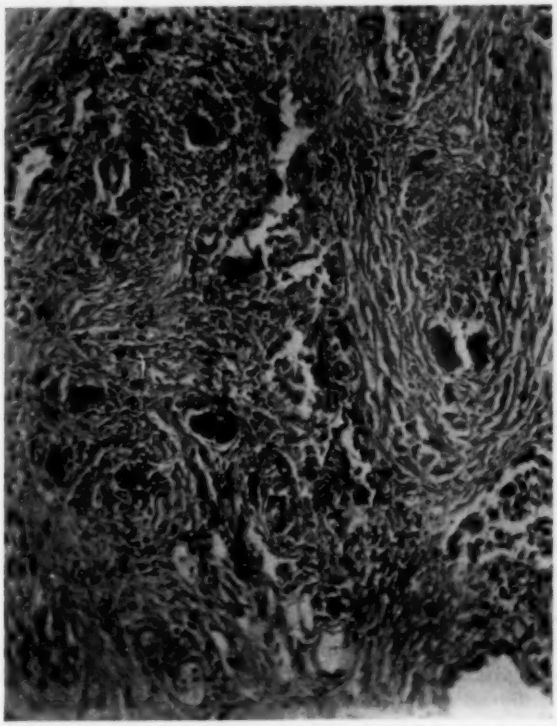

FIG. 2 *B*. Section of lung (× 100) shows more recent similar lesions with adjacent acute cellular reaction.

sections of lung a more acute exudate is present in bronchioles and alveoli. There is both chronic and acute bronchiectasis. *Spleen*. The spleen contains numerous hyaline scars which undoubtedly had been lesions. A few still contain giant cells, and a few younger ones are present made up of epithelioid cells. The same lesions are present in the lymph nodes examined from the mediastinum. *Liver*. Scattered conglomerate tubercles are present throughout the liver, and are essentially the same structure as those described elsewhere. There is some recent acute passive congestion. *Kidney*. A section contains one of the infarcts described. This is made up of conglomerate tubercles among which are many giant cells. It represents a septic infarction, presumably from the lungs.

"*Pathologic Diagnoses:* (1) moniliasis (blastomycosis) of the lungs, (2) metastatic lesions in lymph nodes, liver, spleen, and kidneys, (3) cardiac hypertrophy, with right ventricular preponderance."

Comment: In this patient, the disease was systemic in its pathologic findings but primarily pulmonary in its clinical manifestations. Although an autopsy was done, the cause of death was not clearly understood; it may have been a result of postoperative complications rather than of moniliasis. The prolonged course of the disease, the generally fair condition of the patient at the time of death and the suddenness of his death suggest a diagnosis of chronic pulmonary moniliasis with death due to secondary or complicating factors. The appearance of the older lesions indicated that healing by fibrosis was occurring; probably there was functional adequacy of the remaining tissues. The absence of organisms in the histologic specimens may have been due to the influence of treatment and the natural processes of healing during the long course of the disease.

There is also the possibility that this patient may have had a chronic granuloma due to some cause other than that of infection by Monilia. The constant presence of *C. albicans* and the absence of other pathogenic agents suggest, however, that the diagnosis of moniliasis was correct. The right ventricular hypertrophy was definite evidence of prolonged increased pulmonary artery pressure and can be related to the marked pulmonary infiltration observed clinically and at autopsy. The opinion of Grossi and Balog [48] that evidence of right heart failure is related to toxic myocarditis is not confirmed in this case.

In summary, this case is an example of a disseminated moniliasis which probably began and was most remarkable as a pulmonary disease. The cause of death was not evident, but an autopsy revealed the widespread dissemination of the lesions and illustrated the fact that lesions of this type develop fibrosis as they heal. The case also showed that such fibrosis, when it is widespread or involves important structures, may cause mechanical interference with function.

Case 4. A 56 year old white housewife had had increasing subglottic pain and irritation for two years. The symptoms occurred in episodes of several days' duration and were usually accompanied by wheezing. Several months before entry into the hospital she developed a nonproductive morning cough and intensification of the pain. Later, dyspnea developed, and the cough became productive of a small amount of mucoid sputum. Examination at that time revealed a few crackles over the anterior portion of the right side of the chest. No lesions were seen in roentgenograms of the chest. Microscopic examination of the sputum was negative for pathogenic organisms.

Shortly thereafter the patient felt marked fatigue, and persistent cyanosis of her lips and finger tips appeared. Râles were heard at the base of the right lung, both posteriorly and anteriorly. There was an elevated sedimentation rate. Urine and sputum specimens were normal; serologic tests for syphilis were negative. The patient's temperature became elevated, and râles developed in the anterior portion of the chest on the lower left side. Roentgenographic examination of the chest showed a definite pneumonitis throughout the middle third of each lung field, which extended on the right to the first anterior interspace and possibly the base.

Two weeks later, in June, 1935, the patient became severely and acutely ill with a septic type of fever, during which her temperature rose daily to 104° F. Urine

specimens and blood counts were normal. The sputum became blood tinged, but specimens remained negative for acid-fast organisms. On four successive occasions, *C. albicans* was cultured from sputum specimens and from direct swabs of the pharynx. Chest roentgenograms revealed a diffuse pneumonitis, the shadows of which suggested definite bronchiolitis. She was then seen by one of us (W. J. K.). The patient now showed increased cyanosis on any slight exertion. There were many consonating inspiratory râles over the anterior portion of the left side of the chest, with dullness at the hilus. The right side of the chest was relatively clear. A diagnosis was made of probable Monilia infection, and treatment was started. Potassium iodide alone was given for one week; later, thymol and tartar emetic were added. The patient gained weight, her temperature gradually subsided to normal, her cyanosis and dyspnea disappeared, and she felt well.

The patient was next seen in 1941, when she complained of dyspnea on exertion during the preceding three years. She was no longer cyanotic. A nonproductive cough was present only with exertion. A_2 was greater than P_2. There were bilateral axillary râles, similar to those heard in emphysema, although the expiratory phase was not prolonged. Potassium iodide was then prescribed and was taken for one year. At the end of that time, the exertional dyspnea was improved and there was no cough or sputum. A_2 was still equal to P_2. When last seen in 1948, the patient complained of dyspnea, although there was no cyanosis. P_2 had now become greater than A_2.

Chest roentgenograms made in 1942 and again in 1948 showed only a generalized fibrosis, most marked in the lower halves of the lung fields. An electrocardiogram made in 1948 was characteristic of left bundle branch block.

At the time the patient was first seen, sputum specimens were cultured and *C. albicans* was isolated. A rabbit died after being inoculated intravenously with 5 million cells per 100 gm. of body weight; no characteristic lesions in any organs were seen at autopsy. Direct smears from the spleen and kidneys showed numerous conidia and branching mycelia. Severe pulmonary hemorrhages with adhesions to the pleural wall were present. Nine months and again one year after the onset of the illness, precipitin tests of the patient's serum against *C. albicans* were negative.

Comment: This case illustrates the course of one of the more severe forms of pulmonary moniliasis. After recovery from the initial infection the patient was relatively well, despite the pulmonary fibrosis and the limitations of her respiratory reserve. Her response to iodides, thymol and tartar emetic was satisfactory. The case demonstrates the diagnostic criteria already noted, the disabling after-effects of the infection and the residual fibrosis, and the long, relatively benign course the disease ordinarily follows in the majority of patients.

Case 5. A 55 year old white female had a three-year history of extensive contact with alfalfa meal and dust from chicken coops. Her health remained good until February, 1940, at which time she contracted a severe "cold." The resultant cough persisted and became severe. Eight months later it became productive of large amounts of foamy clear thin sputum, which continued until her entry into the clinic. Four months before admission, the patient had a small hemoptysis; two weeks before entry, she developed slight dyspnea. In the six months before entering the clinic she lost 10 pounds of weight. There was no history of fever at any time. Chest roentgenograms in another hospital in March, 1941, showed "a possible fungous type of infection in the lung."

The patient entered the Medical Clinic in April, 1941. On physical examination, the upper portion of each lung field was found to be essentially normal, but over the lower portion there were increased fremitus and loud crepitant râles, accompanied by varying degrees of amphoric and tubular breathing.

Laboratory examination of the blood revealed a normal count and sedimentation rate. Complement fixation tests for syphilis were negative. Roentgenographic examination of the chest showed the lower half of each lung field to be obscured by a dense opacity of finely granular appearance which gradually shaded into a clear upper lung field.

A bronchoscopy was performed. The tissues appeared reddened and edematous, but no bronchial abnormalities could be demonstrated with lipiodol studies. A profuse discharge of foamy consistency was seen. No pathogenic organisms were found in cultures and smears from an aspirated specimen of the discharge.

A clinical diagnosis was made of probable bronchopulmonary mycosis. No specific therapy was advised.

In a letter dated July 30, 1943, the patient stated that she had suffered a severe respiratory infection during the preceding winter. Because of severe dyspnea and cough, she was now a complete invalid.

Comment: While unproved mycologically, this case shows certain aspects in accord with a clinical diagnosis of bronchopulmonary moniliasis and suggests the factor of repeated infections. One may consider the patient's final complaints of dyspnea and cough as related to fibrosis, although such an explanation overlooks other causes for these symptoms. However, the clinical course and physical and roentgenographic findings are suggestive of a prelude to more chronic fibrosing lesions. The relationship of the dust exposure and the onset of the respiratory complaints recalls the occupational factor in the original description of the disease known as "tea taster's cough" [1] and the more recent work on "thresher's lung." [3, 4] The findings in this patient are also suggestive of those of sarcoidosis. Again one is tempted to speculate on the apparent relationship between these uncommon granulomatous infections and sarcoidosis, although anything more than speculation is unwarranted.

In summary, although the diagnosis of moniliasis was not proved in this case, the findings in the patient are consistent in many clinical aspects with those reported in proved cases and in the literature.

Case 6. A 33 year old white aviator had had sinusitis for 10 years. This complaint became worse in 1940, when he was sent to England to do high altitude flying. About four months after his arrival overseas he developed a slightly productive cough; about a year later, he became conscious of minimal exertional dyspnea. In January, 1942, he was returned to Canada, where he was hospitalized with a very severe bronchitis and laryngitis. He improved sufficiently without specific therapy to return to duty, and was transferred from a relatively dry atmosphere to the damp climate of the Great Lakes.

In June, 1943, the patient complained of morning cough and sputum and increasing fatigue. A mild form of tuberculosis was suspected on the basis of a thoracic roentgenogram. He was hospitalized in February, 1944, at which time he ran a low-grade fever for about one month. A diagnosis of extensive pulmonary fibrosis was then made. He was sent to another hospital; sputum specimens taken there revealed only *C. albicans.*

In June, 1944, the patient was sent to Duke University Hospital, where a specimen of lymph node taken at biopsy was interpreted as consistent with sarcoidosis. Roentgenographic examination of bony structures in May showed no evidence of sarcoidosis. *C. albicans* was recovered from his sputum and gastric washings; a skin test for Monilia was slightly positive. A diagnosis was made of sarcoidosis with secondary *C. albicans* infection, and the patient was started on a course of vaccine therapy. He returned to Canada, where a bronchoscopy was performed. No organisms were recovered from the intratracheal aspiration specimens. He then came to California for treatment. At that time his only symptom was severe dyspnea.

TABLE I

Case 6

	June 1944	Nov. 1944	April 1945	Dec. 1945	Feb. 1946	April 1946	Aug. 1946	Jan. 1947	May 1947	Nov. 1947
Cultures										
Sputum—acid fast	−					−				
Sputum—*C. albicans*	+	+	+	−+	+	+		+		−
Gastric washings—*C. albicans*		+	+							
Urine—*C. albicans*			−							
Urine—routine analysis		n	n	n		n				n
Blood										
Hgb. (gm./100 c.c. blood)	15	14.5	14.5	15		15.5	14	19.4		15
RBC ($\times 10^6$)	5	4.5	4.7	5		5	4.4	6.11		5
WBC ($\times 1000$)			6.45			7.6				8.3
Diff: Eosinophils only, in %			8			5				6
Sed. Rate (Wintrobe)			n			n				n
Serum Proteins										
Total gm. %						6.52				
Alb. gm. %						4.06				
Glob. gm. %						2.46				
Skin Tests										
Tuberculin 1:100						−				
Coccidioidin 1:100		−								
Complement Fixation										
Syphilis	−									
Coccidioidomycosis	−									
Agglutination										
Monilia	−									
Vital Capacity (liter)			2.2	2.2	1.9	1.7	2.25	2.2	1.5	1.5

Code: + positive
− negative
n normal

The patient entered the University of California Hospital (service of W. J. K.) on April 16, 1945. On physical examination, there were slight dyspnea and moderate clubbing of the fingers. Heart sounds were of good quality; A_2 was greater than P_2. Major pulmonary abnormalities were noted in the right upper lobe anteriorly and in the right posterior lung fields, where inspiratory sounds were depressed as compared with those on the left. Below the clavicles anteriorly, inspiratory sounds were

harsher on the right side than on the left. There were a few inguinal nodes and one small nontender right axillary lymph node.

Laboratory studies made during the initial and subsequent entries are summarized in table 1.

The subsequent course of the patient was as follows: Administration of ammonium chloride was begun in April, 1945, but had no appreciable effect. Intramuscular injections of penicillin (2,900,000 units in divided doses) in November, 1945, gave only slight relief. P_2 was greater than A_2 between April and November but became reversed after the administration of penicillin. The patient began penicillin aerosol therapy at home but discontinued it when giant urticaria appeared after the use of 1,000,000 units. In February, 1946, he developed an upper respiratory infection with severe distress. By April, dyspnea, paroxysmal cough productive of thick mucoid yellow sputum, and a generally unsatisfactory course were thought to warrant another trial of penicillin. All symptoms cleared, although a few musical râles over the anterior portion of the left side of the chest and crepitant râles over the deep right subscapular region remained. Clubbing of the fingers became more pronounced.

Conant and his associates [18] have stressed the importance of determining the degree of sensitivity of a patient to *C. albicans* before starting therapy with potassium iodide. These investigators have indicated that the administration of iodides to hypersensitive persons may lead to exacerbations of symptoms and spread of the infection. With these cautions in mind, the patient was given a skin test with standardized heat-killed autogenous *C. albicans* vaccine to determine his sensitivity to the fungus. The erythematous reaction which developed measured 2.5 by 3.4 cm., indicating sensitivity. It was decided to attempt to desensitize the patient before iodides were administered by giving gradually increasing amounts of diluted vaccine. The dilutions employed and the regimen of dosage were essentially those used by Conant and his associates for the desensitization of patients with North American blastomycosis.

The patient received injections of vaccine for six months, with dilutions ranging from 1:100,000 to 1:100, starting in April, 1946. Since at times rather severe reactions occurred with the latter dilution, stronger dilutions were not used. Periodic skin tests performed during the first 11 weeks of administration of the vaccine indicated no reduction in the size of the erythematous reaction. Although no apparent desensitization had occurred, potassium iodide therapy was instituted. After two months, the therapy was stopped because of increased sensitization to the vaccine. The use of potassium iodide was resumed after a rest period of two months, during which time the skin test reactions became appreciably reduced in size. The patient developed dyspnea and cough, which were thought due to the use of iodides, and the medication was again stopped. Further use of *C. albicans* vaccine was discontinued, since there were no indications of desensitization to the fungus.

Hiatt and Martin [43] reported the dramatic recovery of a patient with pulmonary moniliasis following the administration of small amounts of immune rabbit serum. They indicated that serum therapy is of use only when the patient has few or no circulating antibodies demonstrable by serologic tests and when the skin test is negative. Nevertheless, it was decided to use this type of therapy, since our patient not only had failed to become desensitized but also had not responded to the various therapeutic procedures which had been employed.

An anti-*Candida albicans* rabbit serum was prepared with the organisms isolated from the patient's sputum. No reaction occurred when 0.1 c.c. of normal rabbit serum was injected intracutaneously. The patient was given a series of subcutaneous injections of the immune serum, starting with 0.1 c.c. of a 1:10 dilution and increasing the amount by 0.1 c.c. until a final dose of 1 c.c. was reached. During a repeti-

tion of this series of injections, severe local reactions developed and sputum and wheezing increased. The administration of the antiserum was discontinued. Subsequently, a 1:100,000 dilution of the antiserum was employed, followed by dilutions of 1:10,000, 1:1,000, 1:100, and finally by 1:10. There were minor fluctuations in the condition of the patient during the period of administration, but no overall improvement was evident. The patient was afebrile throughout the entire course, with the exception of slight fever during periods of exacerbation of symptoms.

In addition to the roentgenographic examinations in Canada, a chest film made here on April 17, 1945, showed a widespread inflammatory process, without cavitation, significant fibrosis or nodulation. Repeated examinations revealed no appreciable change until January 17, 1946, when there was thought to be some decrease in the inflammatory process. Again there was no change until June 9, 1947, when there was thought to be a slight increase in fibrosis. Chest roentgenograms made in August and October, 1947 were unchanged.

An electrocardiogram in May, 1944 showed slight right axis deviation, with a high takeoff and coving of ST II and III. Another, in April, 1945, showed an unusual record of no characteristic pattern, with an unusual contour of all T waves, suggestive of myocardial disease. Serial records were always similar, varying slightly toward and away from normal. On January 17, 1946, the record was borderline, with flat T_1, diphasic T V4, and R/S ratio small in V5 and V6, suggesting an early pattern of right ventricular hypertrophy. There have been no subsequent tracings.

A letter was received from the patient in the spring of 1949, in which he stated that there had been no change in his general condition. No further examinations have been performed.

Comment: In this interesting case, the illness of the patient illustrates the long chronic course, marked by continual remissions and exacerbations, which the disease may take. The patient's complaints and all objective findings have always been related to pulmonary lesions. His sputum has been consistently positive for *C. albicans* but negative for acid-fast and other pathogenic organisms. The combination of sputum findings, clinical course and chest roentgenograms strongly suggests the diagnosis of pulmonary moniliasis. These same findings, together with the lymph node biopsy, are strongly suggestive of sarcoidosis. The difficulty raised by the conflict of the biopsy diagnosis of sarcoidosis and the clinical impression of pulmonary moniliasis is not great. Each disease has granulomatous lesions of fairly similar pathologic appearance, especially those stages in *C. albicans* infections where there may be no tissue destruction. Mallory [49] has noted that pulmonary fibrosis may be an end result of sarcoidosis. As previously mentioned, it is also the common result of healing in moniliasis. The clinical courses of sarcoidosis and moniliasis also are often similar. The possible relationship of these conditions is emphasized by this case. Such considerations are provocative and tempt one to the thesis that sarcoidosis may be a form of moniliasis or some other fungous infection.[5] If the work of Teilum [50] is authoritative, however, sarcoidosis would appear to be a tissue reaction in the reticuloendothelial system, with minimal necrosis and no caseation in the lesions. Moniliasis, on the other hand, is an invasion of structures by organisms with subsequent destruction of tissue and healing by fibrosis.

This case demonstrates clearly the difficulties encountered in treatment. Adequate doses of iodides, autogenous *C. albicans* vaccine, and anti-*Candida albicans* rabbit serum were used without beneficial results. Penicillin gave temporary relief during periods of exacerbation. Because penicillin is ineffective against *C. albicans*, it is probable that the effect was related to successful treatment of secondary infections. Two points of interest were emphasized by this case: (1) the existence of hypersensitivity to the organisms, and (2) the need for desensitization.

Conclusions

It is true that the concept of pulmonary moniliasis as a primary disease entity has not been accepted universally. As shown in the review of the literature and as illustrated by the six cases, however, there is strong evidence that the organisms are pathogenic in man and capable of producing the lesions and clinical findings described. The controversial question of whether an infection is primary or secondary is of little consequence in view of the demonstrated pathogenicity of *C. albicans*. The important feature, as has been stressed repeatedly, is that the infections, while not immediately fatal, are serious, the end results of widespread tissue destruction and fibrosis are crippling, and the patients are impaired physically, psychologically, socially and economically.

The diagnosis of pulmonary moniliasis is not without difficulty. The clinical aspects of such infections are neither clear-cut nor in themselves specific. Chest roentgenograms may suggest the diagnosis, but the diagnosis can be made only from the proper examination of carefully collected sputum specimens. Studies for pathogens other than *C. albicans* must be exhaustive.

As demonstrated in the literature and by our cases, treatment is difficult and largely empiric. It is varied, and no single measure is uniformly successful. The most useful therapeutic agents at the present time are the iodides and vaccines. While the need for caution in the presence of suspected or recent tuberculosis has been stressed, it may be possible to avoid the danger of fatal dissemination of *M. tuberculosis* by the concomitant administration of streptomycin and iodides.[42] Antibiotics have been tried unsuccessfully, but with the development of more of these agents in the future it is to be hoped that a specific one may be found.

Summary

1. A review of the literature on pulmonary moniliasis is presented.

2. Clinical data on six patients, with notes on the postmortem findings in one case, are described to illustrate the characteristics of the disease and the difficulties encountered in diagnosis and treatment.

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VASOPRESSOR COMPONENTS OF PHEOCHROMOCYTOMAS *

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THE purpose of this report is to present analyses of the pressor amine content of two pheochromocytomas and the metabolism of the hypertensive agents in these and a third tumor. Probably none of the reports of the epinephrine content of pheochromocytomas prior to the past few months is valid, qualitatively. The lack of specificity of the bioassay or chemical methods as they were used in the past did not differentiate that hormone from related compounds having similar biologic or chemical properties. Present evidence indicates that epinephrine may not even be the predominant pressor agent in some of these tumors. The basic advances in the physiology of the adrenergic components of the autonomic nervous system that form the background for this research may be presented as follows:

Recently, a number of reports have appeared in rapid succession that have tended to clarify a long-standing confusion regarding the chemical mediation of so-called adrenergic nerve impulses. Likewise, uncertainty pertaining to the pathway for the biosynthesis of epinephrine seems to be undergoing resolution. This ambiguity arose many years ago when attempts were made to identify with a single chemical entity the actions of the hypothetic sympathins E and I which Cannon and Rosenblueth [1] proposed as the humoral transmitters of nerve impulses from the thoracolumbar division of the autonomic nervous system to the organs which they activated.

After Abel isolated and partially characterized epinephrine,[2] it was conceded generally to be the pressor component of the adrenal medulla. Although the identity of epinephrine with sympathin had its proponents,[3] the pharmacologic properties of the hormone could not be reconciled entirely with the response to sympathetic nerve stimulation.

This discrepancy was anticipated by Barger and Dale,[4] who synthesized and studied a large number of beta-phenylethylamine analogs. They established the very general similarity of the action of these drugs to the response to sympathetic nerve stimulation and designated them *sympathomimetic amines*. These authors also pointed out that none of the compounds, including epinephrine and dl-nor-epinephrine, reproduced faithfully all the adrenergic effects of thoracolumbar nerve stimulation.[4] Many of the subsequent investigators focused attention on points of similarity between drug and nerve action, setting aside until recently the reconciliation of incon-

* Received for publication March 24, 1950.
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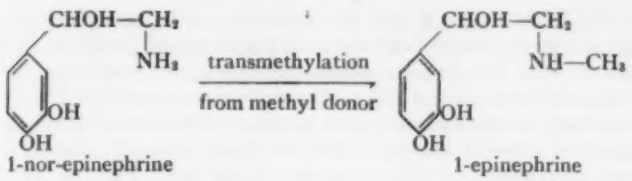
sistencies between the two effects. Although Barger and Dale described the principal biologic methods for distinguishing between epinephrine and its non-methylated counterpart in 1910, the latter compound (nor-epinephrine, nor-adrenaline or arterenol) was later proposed by Bacq [5] and reiterated by others as the compound that most closely simulated the properties of sympathin E.[6]

The seeming discrepancies between epinephrine and nor-epinephrine as the chemical mediator of adrenergic nerve impulses appear to have been resolved, at least from the viewpoints of the more active investigators in this field. Superficially it would appear that, on stimulation, some sympathetic nerves liberate only nor-epinephrine,[7] others yield only epinephrine,[3] and still other adrenergic nerves liberate mixtures of epinephrine and nor-epinephrine.[8] Information up to this point was presented concisely in a recent editorial in the British Medical Journal.[9]

It is probable that the complexity of the chemical mediation of adrenergic nerve impulses is not so great as it would seem to be from the evidence just cited. It is more likely that almost all adrenergic nerves are capable of transmethylating nor-epinephrine more or less quantitatively. Thus the amount of epinephrine appearing in perfusates or extracts of such nerves or other tissues would depend on the balance between the rate of synthesis of nor-epinephrine and its rate of methylation under the prevailing conditions. Bülbring and Burn have indicated that during prolonged splanchnic nerve stimulation of the adrenals, the proportion of epinephrine to nor-epinephrine secreted thereby decreased over the course of time, unless extra methionine was available for transmethylation,[10] which brings us to the problem of epinephrine synthesis in the adrenal gland.

The preponderance of present data indicates that epinephrine is formed directly by the transmethylation of nor-epinephrine. There is strong evidence that this process can occur in the adrenal medulla. Blaschko pointed out the likelihood of the occurrence of this reaction several years ago,[11] and Beyer concurred with this belief when he presented alternate pathways for the biosynthesis which yielded arterenol as the immediate precursor of epinephrine, regardless of the steps leading to arterenol formation.[12] Various investigators have demonstrated the presence of both nor-epinephrine and epinephrine in the adrenals of the pig,[13] the dog,[14] the cow [15] and man.[15a, 15b, 16] U.S.P. epinephrine reference standard has been shown to contain 16 to 18 per cent arterenol.[15c, 15d] Recently du Vigneaud and his associates fed C^{14} radiomethylmethionine to rats and succeeded in isolating from their adrenals epinephrine bearing a radioactive methyl group.[17] Bülbring and Burn have presented in vivo and in vitro evidence to show that transmethylation of nor-epinephrine took place in the adrenal gland.[18] The last step in the biosynthesis of epinephrine in the adrenal medulla, and presumably at the termination of those adrenergic nerves that liberate epinephrine, may be represented as follows:



1-nor-epinephrine 1-epinephrine

Transmethylation of nor-epinephrine as the final step in the synthesis of epinephrine seems the more secure since Holtz and Kroneberg [19] have concurred with this point of view in their recent communication on this subject. Previously Holtz and his associates [20] interpreted their evidence to indicate that epinine, N-methyl-β (3,4-dihydroxyphenyl) ethylamine, was the immediate precursor of epinephrine. This latter point of view had placed the introduction of the hydroxyl group on the side chain as the final step in the synthesis of epinephrine. Alternative theories for the biosynthesis of adrenalin and their documentations have been reviewed by Beyer.[12, 21]

Recent evidence has indicated that the transmethylation of arterenol to adrenalin in the adrenal medulla may be impaired in the pheochromocytoma, leading to the accumulation of nor-epinephrine. Holton,[16b] and Goldenberg et al.[15b] have reported the nor-epinephrine content of these glands composes roughly 50 to 90 per cent of the pressor material. Indeed, Goldenberg [22] has suggested that essential hypertension may be a disease of deficient transmethylation of nor-epinephrine. Data presented herein are consistent with an impairment of nor-epinephrine transmethylation.

Another vasopressor component of the pheochromocytoma was described by Pitcairn and Youmans [23] as being essentially different from either of the aforementioned amines. They regarded the agent as having the nature of hypertensin, principally because the pressor actions could not be abolished by the previous administration of large amounts of an adrenolytic agent, Dibenamine.*

We have had an opportunity to determine the vasopressor components of two pheochromocytomas since the publication of the previous reports. Thus it has been possible to evaluate the relative occurrence of these several pressor agents in the tumors referred to us. Previously this laboratory had an opportunity to examine another pheochromocytoma and urine samples from the patient for metabolic products of "epinephrine."

Case Reports

Case 1. A 43-year-old white woman was referred to the University of Pennsylvania Hospital with a chief complaint of severe paroxysmal headache. The history and physical examination were consistent with the diagnosis of a pheochromocytoma of the right adrenal. The probable period of progression of the condition was five years. The diagnosis was confirmed histologically after surgical excision of the 61.5 gm. tumor. Since a more complete presentation of this case will be given

* Dibenamine is the trademark applied to N,N-dibenzyl-beta-chloroethylamine hydrochloride by Smith, Kline and French.

elsewhere by Dr. R. L. Mayock and his associates, who sent the tumor to us, we will call attention only to certain laboratory findings that are pertinent to the diagnosis.

Preoperatively, the intravenous administration of benzodioxane (20 mg. total; 0.5 mg./kg.) resulted in a prompt fall in blood pressure from 240/150 to 140/70 mm. Hg, which returned to the initial values within 90 minutes. Whereas 0.5 c.c. of 1:1,000 epinephrine solution had no effect on blood pressure, the subcutaneous injection of 1.0 c.c. caused a blood pressure rise of from 130/100 to 210/140 mm. Hg at the end of 5 minutes. Fasting blood sugar values varied from 114 mg./100 c.c. to 268 mg./100 c.c. during a paroxysm. At such times glycosuria could be demonstrated.

Postoperatively, the benzodioxane test showed a slight fall in blood pressure of equivocal significance. The pressor response to the injection of 0.5 c.c. of 1:1,000 epinephrine solution was negative, but the subcutaneous injection of 1.0 c.c. caused a pressor response greater than that obtained preoperatively. Although the blood pressure following the immediate postoperative adjustments decreased to 120/80 mm. Hg, it rose within the next two weeks and was 160/110 mm. Hg at the time of the patient's discharge from the hospital. Six months later her blood pressure had stabilized below this figure.

TABLE I

Summary of Preoperative and Postoperative Tests on a 160 lb. Female Patient Having a Confirmed Diagnosis of a Pheochromocytoma of the Left Adrenal Gland
(Courtesy of Dr. W. S. Randall and Dr. A. S. Mann, of the Ochsner Clinic, New Orleans)

Test	Dose and Admin.	Preoperative Effects			Postoperative Effects		
		Blood Pressure		Pulse	Blood Pressure		Pulse
		Control	Maximal Effect	Control / Max. Effect	Control	Maximal Effect	Control / Max. Effect
Histamine (base)	0.05 mg. i.v.	128/80	224/130	88/100	114/70	138/86	88/88
Saline	5 c.c. i.v.	154/92	138/90	84/84			
Acetyl-β-methyl choline HCl	25 mg. s.c.	130/84	90/50	84/116			
Benzodioxane	17.7 mg.	110/72	116/64	78/92			
Adrenalin	0.5 mg. s.c.	118/80	132/92	80/76	110/80	106/68	76/80
	1.0 mg. s.c.	118/76	134/86	80/68	106/70	118/64	80/58
	1.5 mg. s.c.	110/70	114/70	72/68			
	2.0 mg. s.c.	114/70	164/84	68/88			
Tetraethylammonium chloride	400 mg. i.v.	128/76	96/56	96/108			

i.v. = intravenous; s.c. = subcutaneous; blood pressure in mm. Hg; pulse rate = per min.
Control / Max. Effect = Pulse rate before and at the greatest change following drug administration.

Case 2. A 40-year-old woman was seen by Dr. W. S. Randall at the Ochsner Clinic on May 26, 1949. Her chief complaint was attacks of severe headache. The history and physical examination were consistent with the diagnosis of a pheochromocytoma. The probable period of progression of the condition was five to six years. Surgical excision of the left adrenal was performed and the diagnosis was confirmed histologically. Since the case will be reported in greater detail by Dr. W. S. Randall, Dr. A. S. Mann and their associates, attention will be directed at this time only to the results of certain diagnostic tests. These tests have been summarized in table 1. The postoperative tests were begun nine days after operation, at which time the patient was afebrile and clinically recovered.

Case 3. A 42-year-old white male was referred to the University of Pennsylvania Hospital with a history of attacks of palpitation, headache, epigastric pain, diaphoresis, lacrimation and salivation. Physical examination and operation revealed a tumor of the right adrenal which was pronounced to be a pheochromocytoma. This case has been described elsewhere in some detail by Mayock and Rose.[24]

Preoperatively, up to 1.5 c.c. of 1:1,000 epinephrine solution injected subcutaneously had no effect on blood pressure. Two and 2.5 c.c. of the solution definitely produced a rise in blood pressure. The injection of 10 mg. of acetyl-β-methyl choline subcutaneously produced an alarming rise in blood pressure. Amyl nitrite produced its usual vasodilator effect.

Postoperatively, the injection of as little as 0.25 c.c. of epinephrine solution produced a marked rise in blood pressure, indicating an increased sensitivity to epinephrine.

Analysis of the tumors: In each instance following its excision, a section of the tumor was taken for histologic examination, and the remainder of the gland was frozen immediately in solid carbon dioxide. The frozen gland was brought to the laboratory or packed in carbon dioxide cakes and shipped to us by air transport. On arrival by plane the material was brought to the laboratory by one of our personnel. Urine samples, when available, were refrigerated and analyzed as soon as possible after they were voided.

For the various analyses a weighed portion of a gland was homogenized in a Potter and Elvehjem homogenizer,[25] using ice cold acidified water, the whole homogenizer being packed in an ice-and-water bath. Following homogenization, the material was made up to a final 1.0 per cent suspension of the tumor. The suspension was filtered and portioned into 10 c.c. aliquots, which were then frozen. When an aliquot was used for analysis it was melted and stored in the refrigerator. Unused portions of the thawed aliquots were discarded. Unused tumor was kept in the solid carbon dioxide chest. The extracts were stable, analytically, under these conditions.

Methods: The chemical analyses of the tumor extract were performed by the method of Beyer and Shapiro [26] as used in these laboratories. This iodoadrenochrom method does not distinguish between β-(3,4-dihydroxyphenyl) ethylamines such as arterenol and epinephrine, but does exclude all unsubstituted phenyl and monophenolic analogs. The analyses were performed with and without acid hydrolysis. The technic of Lavietes [27] was used to determine the relative concentration of drug in extract before and following ultrafiltration.

The amine oxidase referred to hereinafter was prepared from guinea pig liver as described previously by Beyer.[28] The preparation was used while fresh. For a portion of the work the enzyme was inactivated by placing a tube containing an aliquot thereof in boiling water for five minutes. Neither the active nor inactivated enzyme preparations as used in this work affected blood pressure appreciably.

The phenol oxidase was prepared from potatoes as previously described by Beyer.[29] This preparation had little or no effect per se on blood pressure and had

very little endogenous respiration if it was allowed to stand overnight in the refrigerator before use. When the use of inactivated phenol oxidase was indicated, a tube containing an aliquot of the enzyme preparation was placed in a vessel of boiling water for five minutes.

In order for us to follow the inactivation of the adrenal extracts by the enzymes, they were placed in Warburg vessels according to the following proportions:

Phenol oxidase	1.0 c.c.
M/4 Na-K-PO_4 buffer, pH 7.8	0.6–0.8 c.c.
1% tumor extract	0.4–0.2 c.c.
Volume = 2.0 c.c.	
Amine oxidase	1.5 c.c.
M/8 Na-K-PO_4 buffer, pH 7.8	1.0–0.5 c.c.
1% tumor extract	0.5–1.0 c.c.
Volume = 3.0 c.c.	

Experimental conditions: 37° C., air as atmosphere, KOH-paper in center well.

The vessels were attached to the respirometers, equilibrated at 37° C., and the reaction was followed until it seemed certain that there was no longer any oxygen uptake due to oxidation of the tumor contents. Pooled samples from three vessels of (1) enzyme control, (2) heat inactivated enzyme plus tumor extract, and (3) enzyme plus tumor extract were filtered and assayed in the barbiturate-anesthetized dog for their pressor content.

The pressor assays were performed on dogs anesthetized with vinbarbital on which a cervical bilateral vagotomy was performed. The pressor compounds were injected into a femoral vein for a duration of 10 seconds. The adrenolytic agent was injected slowly so as to minimize its depressor effect. The time following the adrenolytic agent at which the various substances were given is indicated in the records, but in all instances it was determined that the vascular response thereafter to epinephrine was depressor before other agents were injected.

Results

The results of the chemical assays of the tumors compared with the pressor assays are presented in table 2. Whereas it has been shown that epinephrine, when administered orally or parenterally, is in large measure inactivated in the body by conjugation,[26, 30] no hydrolyzable conjugate of the amines was found in the adrenal tumors. Although several urine samples from patients 1 and 3 were available for study, free epinephrine or arterenol could not be detected therein in any instance. When a sample of urine (163 c.c.) was taken from the third patient shortly after a hypertensive episode, it was found to contain 0.45 mg./100 c.c. of conjugated drug which could be hydrolyzed and determined colorimetrically as "epinephrine."

It is of some interest that the total chemically determinable content of the tumor homogenate was in a freely diffusible form, not bound on or a part of a protein complex. This may not be taken to mean that within the tumor the pressor component is extracellular, for many cells are ruptured during the homogenization of the tumor extracts. However, it is likely that this manipulation did not alter binding of the amines on protein or

that it destroyed any complex containing the pressor agents that might be thought to exist.

In these studies the biologic assay was found to yield higher values for drug concentration than was indicated by the chemical test. The interpretation of this difference is uncertain. A third set of values for the bioassay may be obtained if one assigns to 1-arterenol a pressor ratio of 1.7 times that of 1-epinephrine, as was reported by Luduena,[31] and assumes the rise in blood pressure to be due to a two-component system composed of 50 per cent arterenol – 50 per cent epinephrine in case 1, and 90 per cent arterenol – 10 per cent epinephrine in case 2. The significance of the percentages in the two-component analysis will be discussed in the next paragraph. It should be pointed out that these tests do not preclude the presence in the gland of additional pressor agents of the nature of these amines, or their precursors, which would not be detected by the chemical method but which would show up in the pressor assay. The differential pressor assay

TABLE II

Summary of the Chemical and Biologic Assays of the Pressor Components of the Pheochromocytomas

Assay	Tumor Content, Mg./Gm. Tissue		
	Case 1	Case 2	Case 3
A. Chemical (26):			
1. Without hydrolysis	6.00	8.17	1.78
2. With acid hydrolysis	6.08	8.05	ca. 1.78
3. Following ultrafiltration, but without hydrolysis	6.30		
B. Biologic, pressor:			
1. Calc. as 1-epinephrine	10.3	11.8	
2. Calc. as 1-arterenol	8.8	8.1	

to be described would not exclude or give any indication as to the plausibility of the occurrence of such agents. Four or five dogs were used for the assays of the pressor principle (s) of each tumor.

Although chromatographic [15b, 16] and biologic [8, 32] methods have been described for the differential assay of nor-epinephrine and epinephrine, they were not in use in this laboratory at the time this study was begun. Dr. M. L. Tainter kindly made available a prepublication copy of the method by Auerbach and Angell for the determination of arterenol in epinephrine.[15d] We were not able to use it on the glandular extracts, although it worked satisfactorily on aqueous mixtures of the two pure compounds. Consequently we resorted to an improvisation that yielded the following results that have seemed reasonably reliable.

Following the administration of graduated doses of 1-epinephrine, 1-arterenol and the tumor extract, an adrenolytic agent, usually Dibenamine,

was injected intravenously in sufficient amount to produce a reversal of the epinephrine response without inducing a complete suppression of the pressor effect of arterenol. Thereafter the injection of a previously equipressor dose of the extract produced a rise or fall in blood pressure intermediate between the extremes of the response to the two reference compounds. The pressor or depressor effect of the extract was then matched by injecting mixtures of the two drugs in varying ratios.

The adequacy with which this differential assay could be performed has been illustrated in table 3, wherein data on the extracts from the tumor of case 1 have been compared in three experiments with 1-arterenol, 1-

TABLE III

Summary of the Differential Pressor Assay of the Pheochromocytoma from Case 1 in Terms of Epinephrine and Arterenol with the Aid of an Adrenolytic Agent, Dibenamine

Dog Kg.	Drug	Dose	Blood Pressure Response		Blood Pressure after 15 Mg./Kg. Dibenamine	
			Control / Drug Effect mm. Hg	Percentage Change	Control / Drug Effect mm. Hg	Percentage Change
12.9	Epi.*	1.0 γ/kg.	134/194	44.8	100/66	−34.0
	Art.†	0.82 γ/kg.	134/200	49.3	95/145	52.6
	Tu. ext.‡	0.15 c.c.	136/200	47.0	90/122	35.6
	Epi.-art. mix.§	1.0 γ/kg.	—	—	88/120	36.4
10.1	Epi.	1.5 γ/kg.	144/210	45.8	140/70	−50.0
	Art.	1.5 γ/kg.	142/216	52.1	141/194	37.5
	Tu. ext.	0.2 c.c.	138/213	54.3	143/120	−16.1
	Epi.-art. mix.	1.5 γ/kg.	—	—	137/82	−40.1
12.7	Epi.	2.0 γ/kg.	132/174	31.8	106/48	−54.7
	Art.	2.46 γ/kg.	130/188	44.6	118/140	18.6
	Tu. ext.	0.5 c.c.	118/175	48.3	104/56	−46.1
	Epi.-art. mix.	3.0 γ/kg.	126/190	50.8	118/64	−45.8

* 1-epinephrine base.
† 1-arterenol base.
‡ 1.0% tumor extract.
§ Epinephrine:arterenol mixture; concentration ratio = 1:1.

epinephrine and a 1:1 mixture of the two drugs. In each instance the response following the injection of the tumor extract was intermediate between those that followed arterenol and epinephrine, and was pressor or depressor depending on the dose and sensitivity of the dog to Dibenamine. In two of the three instances in which comparisons were made, the response to the extract was in almost perfect agreement with that of a 1:1 mixture of 1-arterenol and 1-epinephrine wherein half the equipressor doses of the two agents were combined and injected. In one instance the agreement was not so satisfactory.

Table 4 summarizes the data on the tumor extracts from case 2. In this instance, the pressor effects of the tumor extracts could be reproduced

entirely by 1-arterenol in two of the three assays wherein two different adrenolytic agents were employed. The fact that in the third dog the results indicated that epinephrine was present, or that some unaccountable factor was introduced, has led us to assign an arbitrary value of 90 per cent arterenol to this extract. Some idea of the behavior of this tissue extract and the protocol of an experiment can be gained from figure 1. It may be seen that, following a period for stabilization after the Dibenamine injection, the pressor response to epinephrine was reversed and the response to tissue extract and 1-arterenol were equipressor.

The vasopressor effects of the extracts of the tumors from cases 1 and 2 could be accounted for entirely on the basis of the presence of epinephrine,

TABLE IV

Summary of the Differential Pressor Assay of the Pheochromocytoma from Case 2 in Terms of Epinephrine and Arterenol with the Aid of an Adrenolytic Agent

Dog Kg.	Drug	Dose	Blood Pressure Response		Blood Pressure after Adrenolytic Agent	
			Control / Drug Effect mm. Hg	Percentage Change	Control / Drug Effect mm. Hg	Percentage Change
14.3	Epi.[1]	1.0 γ/kg.	144/186	29.1	144/114	−20.8*
	Art.[2]	1.23 γ/kg.	144/170	18.1	145/174	20.0
	Tu. ext.[3]	0.1 c.c.	170/200	17.6	145/174	20.0
8.8	Epi.	2.5 γ/kg.	150/200	33.3	136/56	−58.8†
	Art.	2.46 γ/kg.	142/198	39.4	141/183	29.8
	Tu. ext.	0.2 c.c.	130/184	41.5	136/176	29.4
10.0	Epi.	4.0 γ/kg.	120/181	50.8	88/43	−51.2†
	Art.	4.51 γ/kg.	88/150	70.4	101/128	26.8
	Tu. ext.	0.4 c.c.	94/154	63.8	94/65	−30.8

[1] 1-epinephrine base.
[2] 1-arterenol base.
[3] 1.0% tumor extract.
* N-Ethyl-N-α-naphthylmethylamino-ethylchloride hydrochloride; 1.0 mg./kg., i.v.
† Dibenamine; 15 mg./kg., i.v.

nor-epinephrine or their precursors. This has been demonstrated by the abolition of all pressor or cardiac effect when the extracts were incubated with amine oxidase or phenol oxidase, as illustrated in figure 2 for the extract from the tumor of case 1. These studies were not carried out on the third case, which was made available at an earlier date.

The *first* (top) tracing of figure 2 illustrates the pressor and chronotropic effect of A, 1-epinephrine, B, 1-arterenol and C, the tumor extract. The numbers under the tracings indicate heart rate before and following the injection in beats/min.

The *second* tracing of figure 2 illustrates A, the pressor and chronotropic effect of the tumor extract when it was incubated with heat-inactivated phenol

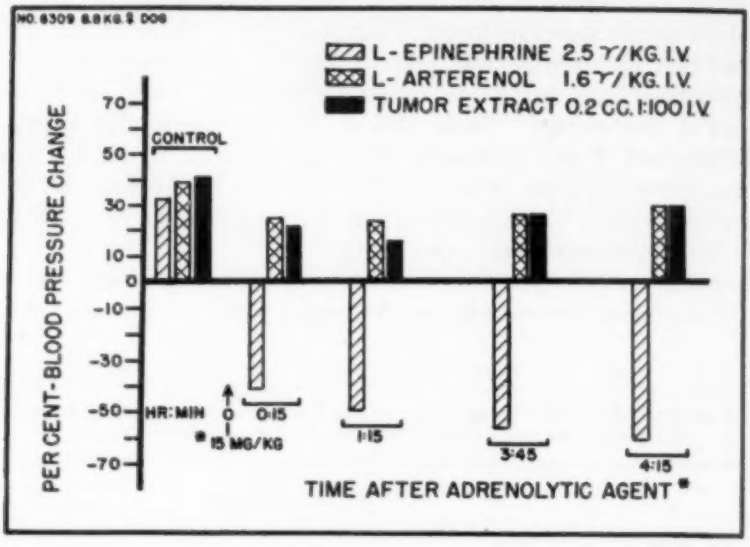


FIG. 1. Diagrammatic representation of an experiment wherein l-epinephrine, l-arterenol and the tumor extract from the pheochromocytoma of case 2 were injected intravenously and the blood pressure response of the dog was measured before and subsequent to the venoclysis of an adrenolytic agent, Dibenamine. Dosages are expressed in terms of the free compound.

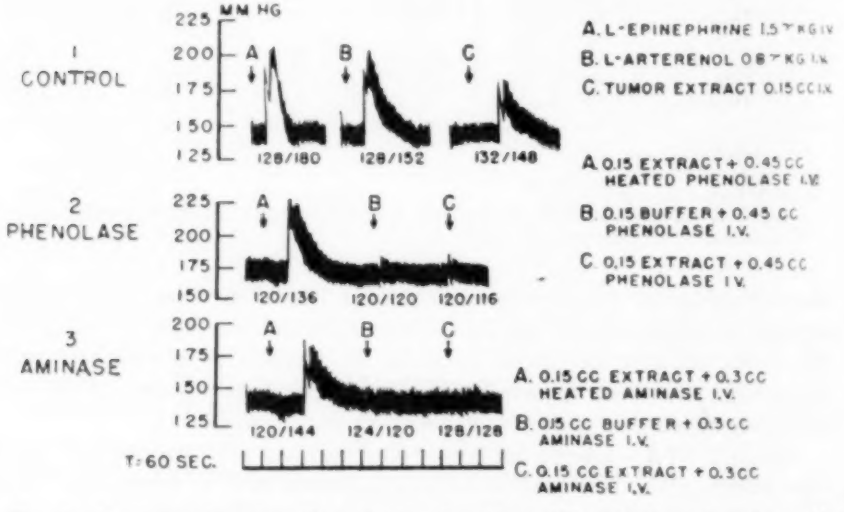
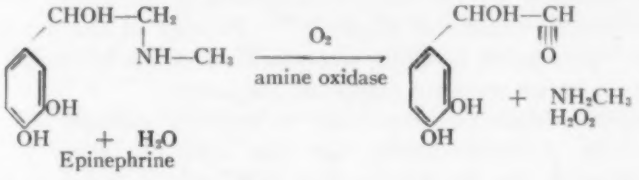


FIG. 2. Demonstrating the effect of phenol oxidase (Phenolase) and amine oxidase (Aminase) on the pressor and chronotropic response to the intravenous injection of a tumor extract. Dosages of epinephrine and arterenol are in terms of the base. See text for discussion.

oxidase (phenolase). When active phenolase was injected at B, it had no effect on heart rate or blood pressure. When active phenolase and tumor extract were incubated and the mixture was injected at C, there was no real effect on blood pressure or heart rate.

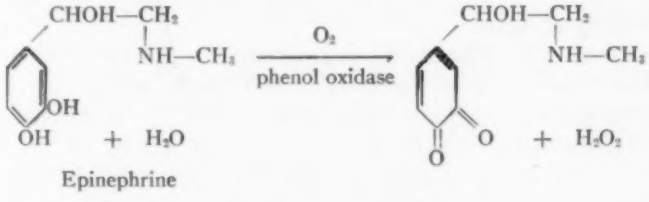
The *third* tracing of figure 2 illustrates the pressor and chronotropic response to the injection A of a mixture of tumor extract incubated with heat-inactivated amine oxidase (aminase). At B, 0.3 c.c. of active amine oxidase was injected intravenously without effect on blood pressure or heart rate. At C, the injection of a mixture of tumor extract incubated with active aminase was without effect on blood pressure or heart rate.

Amine oxidase is capable of activating the oxidative deamination of a number of β-phenylethylamines wherein the amino group is on the terminal carbon atom of the side chain.[28] This applies to both primary and secondary amines. The reaction may be written simply as follows:



The oxidation products of such compounds have no pressor activity.

Phenol oxidase activates the oxidation of the aromatic nucleus of monophenolic or diphenolic β-phenylethylamines.[29] The initial step in the oxidation of epinephrine may be written:



Oxidation products of such a reaction are not pressor agents.

Since all pressor activity was destroyed by either enzyme, it seems likely that the active principles of the tumors must have been catechol-alkylamines such as epinephrine or arterenol. This structural characteristic would exclude the presence of considerable amounts of hypertensin. Amine oxidase has been shown to be different from hypertensinase [33] and angiotonin.[34] We have found that hypertensin was not inactivated by either phenol oxidase or amine oxidase.[35] These results do not necessarily preclude the presence of amino acid precursors of arterenol, such as 3,4-dihydroxyphenylserine or 3,4-dihydroxyphenylalanine, in the extracts.

Comment

A comparison of the above analyses of the vasopressor components of the pheochromocytomas with the results of preoperative examinations permits one to make several correlations of general interest.

It would seem that the most reliable clinical diagnostic test for a pheochromocytoma is the intravenous injection of small amounts of histamine, as was described by Roth and Kvale.[36] If a marked hypertension, together with glycosuria, is observed to follow such injections and if the psychogenic factor can be ruled out, this may be considered strong presumptive evidence for the presence of a pheochromocytoma when the patient's history has suggested the test. Unfortunately, the procedure is quite hazardous, for acetylcholine directly stimulates secretion by the adrenal medulla and histamine does likewise, either directly or indirectly. The use of acetyl-β-methylcholine for this purpose [37] is not so reliable as the other agents and probably is more dangerous because of the longer duration of its action and greater number of effects.[24, 36] Because of the hazard attending the sudden hypertension resulting secondarily from the histamine injection in this condition, other tests are employed frequently.

Although a decreased sensitivity to injected epinephrine is supposed to exist under these conditions, the test does not seem to be entirely reliable. Mayock and Rose have discussed the likelihood of an increased tolerance to epinephrine [24] in these patients. Contradictory to this impression, epinephrine has been used to produce a hypertensive reaction in cases of pheochromocytoma.[38] In view of the fact that both epinephrine and arterenol are released by the tumor, the relative refractoriness to one or the other amine might be of some interest in conjunction with the tests which employ adrenolytic agents.

The response to epinephrine injections can be reversed by doses of sympatholytic agents that have relatively little effect on the pressor action of arterenol or of hepatic nerve stimulation.[1, 7] If, as current research indicates, l-arterenol is liberated to a variable extent at the endings of adrenergic nerves, it is understandable that even relatively potent "adrenolytic" agents might be of limited value in the treatment of neurogenic hypertension. This would be especially true if, as Goldenberg and his associates have suggested,[22] essential hypertension is a disease of impaired transmethylation of arterenol at adrenergic nerve endings.

When a pheochromocytoma contains a preponderance of arterenol, which it presumably is liberating intermittently or continuously, the use of adrenolytic agents such as Benzodioxane or Dibenamine might not be followed by a pronounced fall in blood pressure. This is well illustrated by the negative Benzodioxane test in case 2. Also, the record in figure 2 shows that even fairly large injections of Dibenamine (15 mg./kg.) did not induce a reversal in the blood pressure response to injections of either the extract or arterenol, although the pressor responses to both were diminished.

Although the diagnostic aid of Benzodioxane [39] and Dibenamine [40] is useful if the results are positive, the lack of a fall in blood pressure following the injection of either agent would not be a point of differentiation between neurogenic hypertension and a sustained hypertension [41] caused by a pheochromocytoma which was secreting preponderantly l-arterenol as the pressor amine.

The pharmacologic basis for the use of tetraethylammonium chloride (TEA) as a diagnostic agent for pheochromocytomas seems quite uncertain. LaDue [42] described a case wherein the intravenous injection of 400 mg. of TEA was followed within 30 seconds by a rise in blood pressure from 175/105 to 270/160 mm. Hg, and the elevation persisted for 15 minutes. In the tests performed at the Ochsner Clinic on case 2, using the same dose of TEA, the blood pressure fell from 128/76 to 90/58 mm. of Hg within one minute, rose to 130/92 mm. Hg within two minutes, fell to 96/56 mm. of Hg at four minutes and returned to 124/88 mm. of Hg within eight minutes following the injection. We may be in error in incorporating four-minute reading in the data for table 1, but the test could not be considered informative in any event.

It is difficult to rationalize the use of TEA as a test compound on the basis of its action as a ganglionic blocking agent, since the etiologic pressor agent in this instance is presumed to be circulating in the blood stream. Perhaps it is pertinent to cite the experience of Page and his associates [43] that the injection of TEA may be followed by a rise or a fall or no change in blood pressure. This might indicate that the vascular response in the pheochromocytoma patient to TEA need not be related to the presence of the tumor. Additional tests in other patients of this type will be necessary before the usefulness of this diagnostic test may be considered to be established.

The fact that we could account for the entire pressor content of these tumors on the basis of the presence of epinephrine and its precursors was disappointing, for the impression of Pitcairn and Youmans [23] that a hypertensin-like substance was to be found in the pheochromocytoma was provocative. In the second case, reliance on the irreversibility of the pressor response to the tumor extract following the injection of large doses of Dibenamine could have led us to a conclusion similar to theirs, for Dibenamine does not reverse the overall pressor response to hypertensin.[44] However, the fact that amine oxidase and phenol oxidase destroyed the pressor activity of both tumors that were tested in this laboratory and do not inactivate hypertensin in like manner [35] would seem to preclude the presence of the latter agent.

Finally, a word of caution should be added regarding the choice of the anesthetic agent that might be used to accompany operation wherein a pheochromocytoma is suspected. Meek, Orth and their collaborators have emphasized that cyclopropane more than all commonly used anesthetic agents

except possibly chloroform, enhances the development of cardiac arrhythmias following the injection of epinephrine or certain other 3,4-dihydroxyphenylethylamines.[45] Since paroxysms of hypertension denoting the inadvertent release of pressor amines occur during the excision of such a tumor, ethyl ether should be a more suitable anesthetic agent. The fact that two of the tumors described herein were removed satisfactorily during cyclopropane anesthesia should not be cited in contradiction to the greater theoretic safety afforded by the use of ether together with suitable premedication.

Summary

Three pheochromocytomas have been available for study. All contained substantial amounts of pressor agents. In the two instances in which differential analyses were performed they were found to contain approximately 50 and 90 per cent of the pressor content as l-nor-epinephrine, judged by bioassay. All the pressor content of the tumors could be accounted for by the presence of l-epinephrine and its precursors. These amines were found to be freely ultrafilterable from tumor homogenates, indicating that they were neither bound on nor a part of more complex structures. No conjugated pressor amine could be found in the tumors and no free compound was detected in the urine. In one instance a conjugated compound having the nature of epinephrine was found to be present in urine obtained during a paroxysm of hypertension.

A correlation between the preoperative diagnostic tests and the vasopressor components of these tumors has been made. The reliability of various diagnostic tests has been discussed in the light of these findings.

The data presented herein are consistent with the hypothesis that arterenol (nor-epinephrine) is the immediate precursor of epinephrine in the body, and that within the pheochromocytoma there is an impairment of that transmethylation reaction.

Acknowledgments

It is a pleasure to acknowledge the receipt from Dr. R. L. Mayock, of the University of Pennsylvania Hospital, of the histories, tumors and urine specimens from case 1 and case 3 referred to herein. Also, we are grateful to Dr. W. S. Randall, of the Ochsner Clinic, New Orleans, for the history and tumor from case 2.

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THE ASSOCIATION OF GRAVES' DISEASE WITH MYASTHENIA GRAVIS, WITH A REPORT OF FIVE CASES *

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Since the introduction of neostigmine [1, 2] as a test for myasthenia gravis, there have been 16 cases [3] of myasthenia gravis associated with Graves' disease reported in the literature. In this same period there have been reported a few cases of Graves' disease with muscular weakness which responded to neostigmine but were considered to be thyrotoxic myopathy. However, Brain's classification of muscular disorders associated with Graves' disease [4] lends validity to the separation of myasthenia gravis from other types of muscular weakness occurring in association with Graves' disease on the basis of the response to neostigmine.

In this paper we present five cases recently observed at Cook County Hospital and considered to be true myasthenia gravis associated with Graves' disease. It is our purpose to point out that this syndrome is not rare and may be easily overlooked or misinterpreted, and to discuss the therapeutic problems involved.

Case Reports

Case 1. A 25 year old Negro female entered Cook County Hospital on May 3, 1948, with complaints of "nervousness," loss of weight, palpitation and exertional dyspnea of two months' duration.

Past history disclosed that she had had numerous admissions to Cook County Hospital and other institutions during the previous six years. In 1944 she had been admitted to the neurologic service of another hospital because of episodes of diplopia and ptosis of the right eyelid. At that time neurologic examination revealed a divergent strabismus, ptosis of the right eyelid and apparent proptosis of the left eye. There were a paralysis of upward gaze in the right eye and slight restriction of the left internal and inferior recti muscles. The pupils were slightly unequal and reacted sluggishly to light and accommodation. Reflexes were generally hyperactive. A fine digital tremor was noted. The patient weighed 170 pounds.

Blood and spinal serologic reactions were negative. Roentgenograms of the skull, chest and optic foramina were normal. Determinations of the basal metabolic rate were plus 45 and plus 48. Serum cholesterol was 180 mg. per 100 c.c.

A medical consultant did not think that the patient had hyperthyroidism. A provisional diagnosis of syphilitic basilar meningitis was made, and the patient was treated with a course of potassium iodide and intramuscular bismuth.

In August, 1946, the patient was admitted to a medical service of Cook County Hospital with complaints similar to those of the present admission. She weighed 115 pounds. Recent diplopia was noted in the systemic inquiry. "Nervous spells" associated with muscular twitchings, tremor of the hands, dyspnea and coughing

* Received for publication March 25, 1950.

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(choking?) were complained of and observed on the initial examination. Symptoms of intolerance to heat and loss of weight in spite of a good appetite were elicited. No cranial nerve palsy was described. The thyroid was not palpable. The basal metabolic rate was consistently elevated, up to plus 56. Cholesterol was 138 mg. per 100 c.c. The patient was considered to have hyperthyroidism and was treated for a period of one month with Lugol's solution and propylthiouracil. There was a gain of weight to 138 pounds. The basal metabolic rate decreased to plus 11, and cholesterol increased to 170 mg. per 100 c.c.

On two short subsequent admissions to Cook County Hospital in 1947, bilateral external ophthalmoplegia, including ptosis of the right lid, was noted. Weight in July 1947 was 119 pounds. The basal metabolic rate was not obtained. Cholesterol was 107 mg. per 100 c.c. The patient complained of dysphagia on both of these admissions.

On May 3, 1948, the patient came under the authors' observation. Physical examination revealed a moderately emaciated, hyperactive, "fidgety" Negro female with moderate exophthalmos and complete external ophthalmoplegia, including bilateral ptosis. Blood pressure was 140 mm. Hg systolic and 70 mm. diastolic, and the pulse was 120. The patient weighed 100 pounds. The palms were hyperhidrotic, but no digital tremor was present. The thyroid was not palpable. The remainder of the physical examination was not remarkable except for generalized slight motor weakness, most noticeable in the left extremities and in the facial musculature. Reflexes were equal bilaterally, and there was no pathologic reflex.

Three consecutive determinations of the basal metabolic rate were plus 66, plus 57, and plus 53. Protein-bound iodine was 11.1 micrograms per 100 c.c. of plasma. Total serum cholesterol was 107 mg. per 100 c.c. Twenty-four hour urinary creatine content was 190 mg. Serum potassium was 13.5 mg. per 100 c.c. (This was not repeated.) Electrocardiogram showed a sinus tachycardia and inversion of the T wave in Lead I, CF_2, CF_4, and CF_6. Roentgenogram of the chest, blood count, urinalysis, non-protein-nitrogen, and blood and spinal fluid serologic reactions were all negative.

Studies with radio-active iodine substantiated the diagnosis of hyperthyroidism. Three millicuries of I_{131} were given orally and 13.8 per cent was excreted in the urine in the first 24 hours, 1.92 per cent in the second 24 hours, and 0.6 per cent in the third 24 hours. An additional dose of 3 mc. was given orally, the total dosage of 6 mc. being considered a therapeutic dose. With the use of a Geiger counter, most of the radio-active iodine was found to be in the region of the thyroid gland four days later.

On May 16 the patient had the first recognized myasthenic crisis. She aspirated a portion of a glass of water because of difficulty in swallowing and became dyspneic, with audible râles in the chest and expectoration of white sputum. Neostigmine, 0.5 mg. intramuscularly, gave marked symptomatic improvement, including partial relief of the external ophthalmoplegia.

The patient was given 15 mg. of neostigmine methylbromide every six hours orally but continued to experience increasingly severe myasthenic crises, characterized by dysarthria, dysphonia, dysphagia, severe generalized peripheral muscular weakness, and respiratory embarrassment requiring full use of accessory muscles of respiration. Dosage of neostigmine was increased until the patient was receiving as much as 300 mg. of neostigmine methylbromide orally daily and as much as 3.75 mg. neostigmine methylsulfate intramuscularly to combat individual crises, which were prone to occur in the early evening or early morning hours. Atropine sulfate, 0.6 mg. every four hours, was necessary to combat abdominal cramps and diarrhea, which occurred as toxic reactions to the neostigmine. In the interim between attacks the patient was fairly comfortable at bed-rest and mild ambulation. The facial expression,

formerly masklike, became animated. The external ophthalmoplegia was at no time completely alleviated, but the ptosis was often not discernible.

Repeated determinations of the basal metabolic rate between June 7 and July 13 ranged between plus 16 and plus 35, with a mean of plus 26. Pulse ranged between 74 and 90. Weight remained stationary at about 100 pounds.

On July 20 the patient went into a myasthenic crisis characterized by severe respiratory distress and, despite large doses of neostigmine and resuscitation measures, died in respiratory failure.

Autopsy revealed a small, firm thyroid gland weighing 15 gm. Histologic examination showed marked acinar hyperplasia and interstitial fibrosis with diffuse infiltration by lymphocytic elements. The thymus weighed 19 gm. and, on microscopic examination, appeared essentially normal, with some predominance of the epithelial elements. Sections of several skeletal muscles revealed a small collection of lymphocytes in one. Examination of the rest of the organs was grossly and microscopically not remarkable, except for dilatation of the cardiac chambers and pulmonary edema.

Case 2. A 35 year old Negro female entered Cook County Hospital on May 5, 1949, with a history of "nervousness," loss of weight (11 pounds) with unimpaired appetite, easy fatigability and minor intolerance to heat for one year. Two months previous to admission, intermittent ptosis of both eyelids and episodic diplopia appeared. A suggestive history of dysphagia, characterized by "choking" on ingestion of food, was obtained.

Past history was noncontributory, except for inadequately treated syphilis.

Physical examination revealed a well developed and well nourished Negro female, not appearing ill and displaying no gross myasthenic phenomenon except for the eye-signs. Pulse rate was 110 and blood pressure was 165 mm. Hg systolic and 85 mm. diastolic. Expressive facial movements were diminished and gross hyperthyroid signs were masked. Pupils were equal and reacted physiologically. Slight exophthalmos of the right eye was present. There was bilateral impairment of lateral, upward and medial gaze (figure 1). No impairment of the functions of the other cranial nerves could be demonstrated. The thyroid gland was diffusely and moderately enlarged. The remainder of the physical examination was negative. No muscular wasting, muscle fasciculation or peripheral paresis were observed.

Serial determinations of the basal metabolic rate ranged between plus 87 and plus 41. Serum cholesterol was 123 mg. per 100 c.c. Roentgen studies showed no evidence of thymic enlargement, disturbance of deglutition, or intracranial disease. Electrocardiogram showed a sinus tachycardia. Kahn and Wassermann reactions in the blood were positive; the serologic reaction and chemical examinations of the spinal fluid were negative. Erythrocyte count was 3,950,000 and hemoglobin, 67 per cent; leukocyte count was 6,400, with a slight polymorphonuclear neutrophilic leukocytosis. Urinalysis was negative.

The myasthenic status was investigated with neostigmine,[5] curare [6] and exercise tests. Neostigmine intravenously in dosage of 0.5 mg. produced partial alleviation of the ophthalmoplegia within several minutes (figure 1). d-Tubocurarine chloride solution (Squibb) injected intravenously in the amount of 0.33 c.c. (one-tenth of the physiologic paralyzing dose) resulted in complete ophthalmoplegia. It was observed that throughout the day the ophthalmoplegia varied in extent, being most improved when the patient was awakened from sleep. Forced exercise of the external ocular muscles resulted in increase of the ophthalmoplegia. No other subjective or objective effect of neostigmine, curare or exercise was noted.

Propylthiouracil was administered from June 8 to August 13, 1949, in dosage up to 400 mg. daily, with a decrease in basal metabolic rate to plus 21, a gain in weight

FIG. 1. Case 2. Column A, before neostigmine; column B, 5 minutes after 0.5 mg. neostigmine methylsulfate intravenously. a, f, frontal gaze; b, g, right lateral gaze; c, h, left lateral gaze; d, i, upward gaze; e, j, downward gaze.

of 20 pounds, and a decrease in pulse rate. The patient refused operation or further medical therapy. Recent telephone conversation with her mother four months after discharge disclosed no apparent change in the patient's clinical status.

Case 3. A 45 year old Negro female entered Cook County Hospital on September 22, 1949, with symptoms of recurrence of a toxic goiter of about one year's duration.

The patient stated she had been "nervous" since 1937. Several years previously she had noted that her eyes were becoming slightly more prominent. In 1939 she experienced a sudden episode of diplopia which persisted intermittently until time of admission. "Choking" spells, with regurgitation of liquids through the nose,

occurred infrequently during this period. In 1942 intermittent ptosis of the eyelids was first noticed. At about the same time the goiter became visible. Lugol's solution was prescribed by a physician and continued for nine months, with alleviation of "nervousness." During this period the patient believes the diplopia and ptosis were improved.

In 1944 increased "nervousness," tremor, polyphagia with slight loss of weight, palpitation, breathlessness and increase in size of the goiter were noted. She refused operation at this time and took Lugol's solution with little effect. In February, 1946, she was admitted to Cook County Hospital with exophthalmic goiter. Determinations of the basal metabolic rate at this time were elevated to plus 35. A subtotal thyroidectomy was performed with good therapeutic result.

In June, 1946, a diagnosis of ocular myasthenia gravis evidently was made at an eye clinic, as neostigmine tablets in dosage of one three times a day were prescribed. The patient continued to take the tablets until April, 1948. However, little or no subjective effect from this medication was noted. Ptosis and diplopia still occurred. During July, 1948, goiter was again noted, with recurrence of "nervousness," palpitation and polyphagia. In January, 1949, the patient reëntered Cook County Hospital with symptoms and signs suggestive of thyrotoxicosis, but this was not substantiated by serial determinations of the basal metabolic rate, which were as low as minus 11. Thyroid extract, 1 gr. daily, was taken from February until May, 1949, when it was discontinued because of a basal metabolic rate of plus 50 and plus 51. In August, 1949, determinations of the basal metabolic rate were plus 1 and plus 8. In September the patient was admitted to the hospital and came under the authors' observation.

Physical examination revealed a well nourished, well developed Negro female, alert and coöperative but not hyperactive. The pulse was 116 and blood pressure 170 mm. Hg systolic and 70 mm. diastolic. Moderate bilateral ptosis of the lids, more marked on the left side, was noted and could be increased by repeated opening and closing of the eyes. Marked restriction of extraocular movements was present, with almost complete paralysis of upward gaze and marked restriction of lateral and inward gaze. When the eyelids were manually raised there appeared to be moderate exophthalmos, more pronounced on the right. Hertel exophthalmometric readings were 27 and 21 mm. for the right and left eye, respectively. The pupils were equal and reacted in accommodation. Funduscopy revealed minimal hypertensive vascular changes.

An old thyroidectomy scar was present. The thyroid gland was visibly moderately enlarged, somewhat firm and suggestively nodular.

The heart was moderately enlarged to the left. The rate was regular and rapid. At the pulmonic area a rasping systolic murmur was heard, followed by an accentuated second pulmonic sound. A fine digital tremor was present, but there was no palmar hyperhidrosis. No gross peripheral myasthenic sign was present. Neurologic examination was negative except for the ophthalmoplegia.

Serial determinations of the basal metabolic rate ranged from plus 17 to plus 32. Serum cholesterol was 130 mg. per 100 c.c. Urinary creatinine excretion in a 24 hour period was 1,041.6 mg., and creatine excretion was 369.6 mg. The Kahn serologic reaction, the serum potassium and non-protein nitrogen were normal. Hemoglobin was 54 per cent, red blood cell count was 3,490,000, and white cell count was 6,400, with a normal differential count.

Roentgen studies failed to reveal evidence of thymic enlargement. The size of the heart was at the upper limits of normal, with a normal contour. Electrocardiogram showed a sinus tachycardia with depressed PQ and ST segments in the limb leads. No evidence of left ventricular hypertrophy or strain was present in the unipolar limb and precordial leads.

The initial neostigmine test, using 0.5 mg. intravenously, failed to affect the ophthalmoplegia. A repetition of the test the next day, using 1.0 mg., showed an unequivocal partial alleviation of the ophthalmoplegia (figure 2f-j). A test of sensitivity to curare, using 0.4 c.c. of d-Tubocurarine solution (Squibb) intravenously, resulted in a complete ophthalmoplegia within a few minutes and some flattening of the facial musculature (figure 2 C, D). No paresis of any of the other muscles supplied by the cranial or peripheral nerves was grossly apparent. The Jolly myasthenic reaction was positive in the abductor digiti quinti and orbicularis oculi muscles, and this was partially alleviated by neostigmine and made worse by curare. Electro-

FIG. 2. Case 3. A, frontal gaze; B, right lateral gaze before curare sensitivity test. C, frontal gaze 5 minutes after 0.4 c.c. d-Tubocurarine solution (Squibb) intravenously; D, right lateral gaze.

Column I, before neostigmine; column II, 5 minutes after 1.0 mg. neostigmine methylsulfate intravenously. a, f, frontal gaze; b, g, left lateral gaze; c, h, right lateral gaze; d, i, upward gaze; e, j, downward gaze.

myographic studies of the orbicularis oculi muscles revealed myasthenic responses (figure 3).

Lugol's solution was administered for two weeks, with a good symptomatic response and a decline of the basal metabolic rate to the range of plus 1 to plus 9. The pulse rate slowed to normal limits and the electrocardiogram reverted to normal. The cardiac murmur subsided. Myasthenic ocular signs were unchanged. Urinary creatinine excretion in a 24 hour period was 998.2 mg. and creatine excretion decreased to 48.3 mg.

A subtotal thyroidectomy was performed on November 2, 1949, with an uneventful postoperative course. Surgical biopsy of the thyroid was compatible with the diagnosis of diffuse toxic goiter. Biopsy of the sternohyoid muscle did not show evidence of lymphorrhages.

Six weeks postoperatively, determinations of the basal metabolic rate were minus 29 and minus 30, and the serum cholesterol had climbed to 375 mg. per 100 c.c. The patient felt well, except for occasional episodes of palpitation. Myasthenic ocular symptoms were unchanged, and the ptosis could still be aggravated by exercise of the lids.

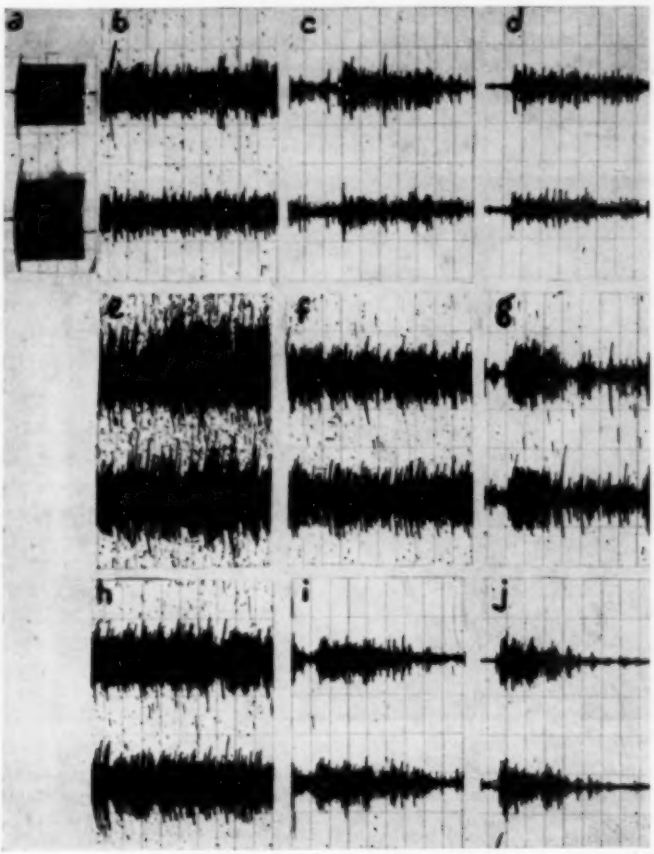

FIG. 3. Case 3. Electromyograph of right (upper tracings) and left (lower tracings) orbicularis oculi muscles during sustained contraction.

a, standardization at 2,000 microvolts; kymograph speed 1 cm. per second, each division equal to 0.5 cm.; b, potential at beginning of sustained contraction; c, 30 seconds later; d, 3 minutes later. e, beginning of sustained contraction 10 minutes after 1.0 mg. neostigmine methylsulfate intravenously; f, 30 seconds later; g, 3 minutes later. h, beginning of sustained contraction 5 minutes after 0.4 c.c. d-Tubocurarine solution intravenously; i, 30 seconds later; j, 3 minutes later.

Case 4. A 57 year old Negro female entered the medical service of Illinois Research and Educational Hospital on August 15, 1949, having been referred by the neurologic service for control of thyrotoxicosis discovered in the course of myasthenia gravis.

Except for asthmatic bronchitis since childhood, the patient had been well until June, 1947, when she visited a local physician because of an upper respiratory infection and asthma. She was told at this time that she had hypertension, and on

subsidence of the asthmatic episode, thyroid extract was prescribed in an attempt to reduce her weight. While on thyroid extract the patient rapidly lost weight (from 198 pounds in June to 140 pounds in September, 1947). Progressive weakness, palpitation and irritability developed about July. Thyroid medication was stopped in September, 1947, but symptoms persisted.

In November, 1947, immediately after an episode of epistaxis, the patient experienced diplopia and ptosis. These symptoms recurred intermittently since that time. Occasional episodes of nasal regurgitation of fluids also occurred.

In January, 1948, the patient became bedridden because of profound weakness. In June, 1948, the patient had a positive neostigmine test for myasthenia gravis at an eye infirmary, and neostigmine methylbromide, 15 mg. every three hours, was prescribed, with partial relief of the generalized muscular weakness. In June, 1949, an elevated basal metabolic rate was discovered at Illinois Neuropsychiatric Institute. Neostigmine requirements rose to 15 mg. every three hours orally and 1 mg. every three hours intramuscularly during the waking hours. It was at this time that the patient was admitted to the medical service of Research and Educational Hospital and, through the courtesy of Dr. R. W. Keeton, was seen by the authors.

On physical examination the patient displayed slight generalized muscular weakness. No muscular atrophy or fasciculation was present.

Pulse was 100 and blood pressure 174 mm. Hg systolic and 92 mm. diastolic. Incomplete external ophthalmoplegia, including bilateral partial ptosis of the eyelid, was present, with absent upward gaze and slightly restricted downward and lateral gaze. Exophthalmos was not apparent. No dysphagia or dysarthria could be demonstrated. Funduscopy showed minimal hypertensive vascular changes. The thyroid gland was small, firm and diffusely palpable. The heart was slightly enlarged, and a grade III systolic murmur was heard over the precordium. Neurologic examination, other than for the ocular signs, was negative. A fine digital tremor and palmar hyperhidrosis were present.

Erythrocyte count was 4,500,000, hemoglobin 9 gm., leukocytes 5,200, with a normal differential count. Urinalysis was negative, as was the serologic reaction in the blood. Serum cholesterol was 192 mg. per 100 c.c., total protein 6.9 mg., and non-protein-nitrogen 31 mg. Twenty-four hour urinary creatinine excretion was 1,272.0 mg., creatine 184.4 mg.

The basal metabolic rate ranged from plus 42 to plus 50. Studies with radioactive iodine showed 82 per cent retention in 24 hours, and 72 per cent of the radioactive iodine in the serum was bound to protein. Hertel exophthalmometer recordings were normal.

Roentgen studies showed no evidence of an enlarged thymus or abnormal deglutition. Roentgenograms of the skull were negative.

A number of muscles were tested for Jolly's myasthenic reaction. The right abductor minimi showed signs of fatigue within 40 seconds but did not completely fail to respond after four minutes. The orbicularis oculi muscle showed a definite Jolly's reaction in 145 seconds (approximately 70 contractions). Electromyography of the orbicularis oculi muscles demonstrated the myasthenic phenomena and the response to neostigmine (figure 4).

Withdrawal of neostigmine resulted in the appearance within nine hours of dysphagia, slight respiratory difficulty and an increase of ophthalmoplegia, all dramatically relieved by administration of 1 mg. of neostigmine intravenously (figure 5).

On October 18, parenteral administration of neostigmine was discontinued and the patient was maintained on 120 mg. of neostigmine methylbromide orally daily. On November 15, the administration of Lugol's solution was started and the patient made a good response in nine days, with a drop in pulse rate to about 80 and a de-

crease in basal metabolic rate to plus 17. Urinary creatine excretion decreased to 33.6 mg. per 24 hour volume. On November 27, propylthiouracil, in dosage of 450 mg. daily, was begun, and by December 21, 1949, the basal metabolic rate was plus 8 and the patient had gained 22 pounds in weight.

With control of the thyrotoxicosis there was increase in general well-being and muscle strength. Neostigmine requirements remained unchanged.

The patient declined operation and was discharged on January 3, 1950, on propylthiouracil and oral neostigmine, to be followed as an out-patient.

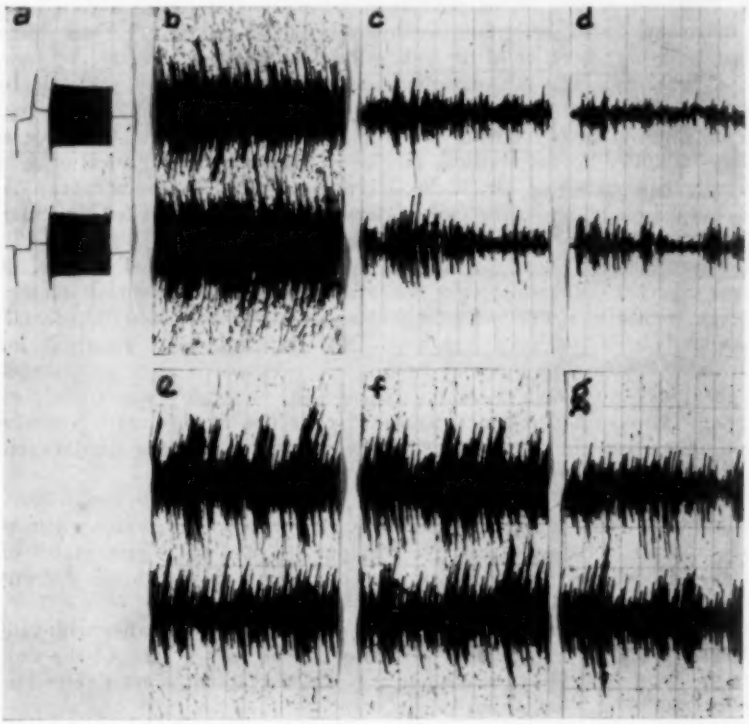

FIG. 4. Case 4. Electromyograph of right (upper tracings) and left (lower tracings) orbicularis oculi muscles during sustained contraction.

a, standardization at 2,000 microvolts, kymograph speed 2.5 cm. per second, each division equal to 0.5 cm.; b, potential at beginning of sustained contraction; c, 30 seconds later; d, 3 minutes later. e, beginning of sustained contraction 10 minutes after 1.0 mg. neostigmine methylsulfate intravenously; f, 30 seconds later; g, 3 minutes later.

Case 5. An 18 year old Negro female entered Cook County Hospital on September 10, 1945, with complaints of "nervousness," "bulging of the eyes" for 16 months, and progressive loss of weight, palpitation and weakness for one month. In August, 1944, she had undergone a subtotal thyroidectomy in Jackson, Mississippi, for a toxic goiter of several months' duration. Symptoms of "nervousness" persisted following operation, and the exophthalmos increased to the point where the eyes were painful. In the three weeks prior to admission the patient had lost 25 pounds in weight, and weakness had become so profound that the patient had become bedridden.

Physical examination revealed an emaciated Negro female who displayed muscular weakness to such a degree that she was unable to turn on her side or sit up in bed. Pulse was 120 and blood pressure 132 mm. Hg systolic and 76 mm. diastolic. Severe bilateral exophthalmos was present with Hertel exophthalmometric readings of 32 and 34 mm. on the right and left, respectively. The conjunctivae were deeply injected but not chemotic. External ocular movements were very limited in all directions. Pupils were equal and reacted to light and accommodation. Ptosis, although not observed on the initial examination, was later noted to be present intermittently. The thyroid gland was diffusely but asymmetrically enlarged. A healed thyroidectomy scar was noted.

The remainder of the physical examination was negative except for extreme weakness of the general body musculature. No muscular fibrillation or fasciculation was observed.

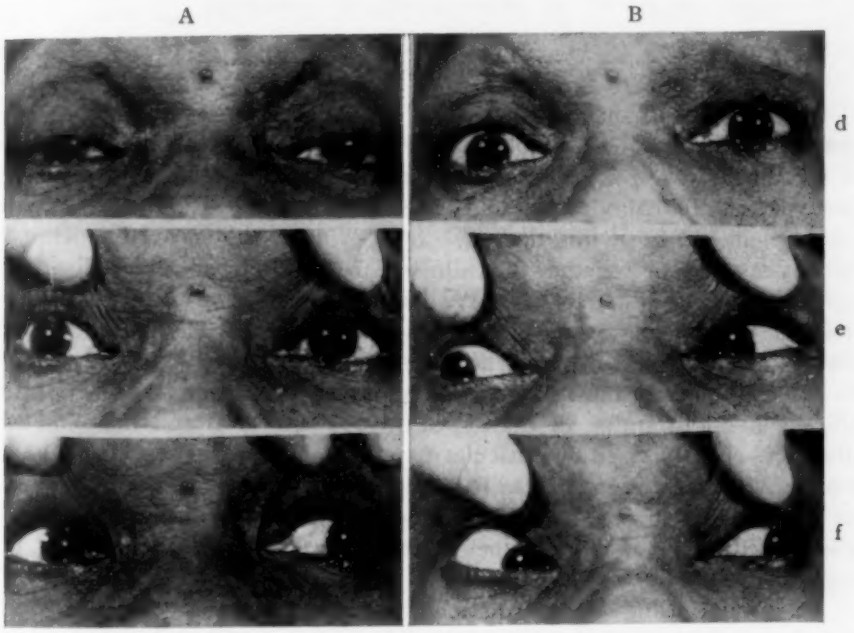

FIG. 5. Case 4. Column A, before neostigmine; column B, 5 minutes after 1.0 mg. neostigmine methylsulfate intravenously. a, d, frontal gaze; b, e, right lateral gaze; c, f, left lateral gaze.

Determinations of the basal metabolic rate were plus 59, plus 29 and plus 26. Serum cholesterol was 155 mg. per 100 c.c. Roentgenograms of the chest showed no evidence of thymic enlargement, and films of the skull were negative. Urinalysis, blood count and Kahn serologic reaction were negative.

A trial of Lugol's solution failed to improve the clinical status. The patient's muscular strength appeared to vary from time to time. Episodes of dysphagia and periods of respiratory difficulty occurred.

On October 22, the intramuscular neostigmine test was positive, with dramatic relief of the peripheral muscular weakness; however, the ophthalmoplegia was not affected. Jolly's myasthenic reaction was present prior to administration of neostigmine in the flexor digitorum sublimis and profundus, complete fatigue occurring

after 30 seconds of faradic stimulation. A muscle biopsy failed to reveal significant changes.

The myasthenia remained under fair control with moderate doses of neostigmine. However, the patient's general condition continued to deteriorate, with a decline in weight from 108 pounds to 90 pounds within several months. A determination of the basal metabolic rate in April, 1946, was plus 26, and serum cholesterol was 140 mg. per 100 c.c. After a gradual downward course, the patient died on June 3, 1946.

Autopsy revealed a persistent thymus weighing 20 gm., which, on microscopic examination, showed slight hyperplasia, particularly of the lymphoid elements. The thyroid gland weighed 40 gm. and, on microscopic examination, showed active acinar hyperplasia and interstitial round cell infiltration. Sections of skeletal muscle showed perivascular and interstitial fatty and round cell infiltration. Other than slight interstitial round cell infiltration in the myocardium and bronchopneumonia, the remainder of the organs were grossly and microscopically not remarkable.

Discussion

External ophthalmoplegia occurs in almost all cases of myasthenia gravis [7, 8] and may be the sole manifestation throughout the entire course of the illness.[9, 10] Brain,[4] Rundle [11] and Means [12] have reported on the occurrence of ophthalmoplegia in Graves' disease, and Rundle has stressed the high incidence of this finding. It is evident, therefore, that when the two diseases occur together it is difficult to determine to which disease the ophthalmoplegia is ascribable. We have used as our criteria for the diagnosis of myasthenia gravis the unequivocal effect of neostigmine on the involved muscles and their marked sensitivity to curare. That the response to neostigmine may not be specific is suggested by observers who report the efficacy of neostigmine in thyrotoxic myopathy [13, 14, 15] and neuromuscular disorders characterized by muscular paresis.[16] The cases reported as thyrotoxic myopathy with response to neostigmine are difficult to evaluate and, as suggested by Eaton,[17] may well have been true myasthenia gravis. The alleged efficacy of neostigmine in neuromuscular disorders other than myasthenia gravis has been challenged by several careful observers.[18, 19]

It is our feeling that dramatic response to neostigmine and sensitivity to curare must be considered, in our present state of knowledge, to be specific diagnostic tests for myasthenia gravis. We have tried these tests in a small series of thyrotoxic patients with muscular weakness of nonspecific nature, such as quadriceps weakness and decrease in power of the hand-grip, without demonstrable effect.*

In uncomplicated myasthenia gravis it has been reported that the basal metabolic rate is either normal or slightly decreased.[21, 22] The use of thyroid extract in the treatment of myasthenia gravis has given conflicting results. Thorner [3a] reported the beneficial effect of thyroid extract in one case of uncomplicated myasthenia gravis, but Eaton [22] believes that thyroid extract

* In this series we used doses of curare up to one-tenth the physiologic paralyzing dose. However, it is recommended that the initial test be performed with one-fortieth the paralyzing dose, since untoward reactions have been reported in myasthenic individuals.[20]

either has no beneficial effect or may increase the muscular weakness. In two of the cases in our series (cases 3 and 4), thyroid extract was administered for prolonged periods. In case 3 no demonstrable effect on the myasthenic state was noted, while in case 4 symptoms of myasthenia gravis occurred during thyroid administration.

Of further interest, and the subject of much controversy in the literature in recent years, is the response of symptoms thought to be those of myasthenia gravis to the medical or surgical therapy of an associated thyrotoxicosis. If, however, we are to take literally the statement of Laurent,[13] whose opinions are evidently shared by Brain,[7] there would be little basis for controversy, since he states that while thyrotoxic myopathy is cured by thyroidectomy, thyroidectomy without thymectomy has never cured myasthenia gravis. The resolution of this controversy is of practical importance, since one school of thought believes that therapy of an associated hyperthyroidism causes myasthenia gravis to become worse,[3a, g, i] not infrequently with a rapidly fatal outcome, while the other feels that therapy of the hyperthyroidism will improve or at least not affect the myasthenia gravis.[3h, 22]

In evaluating the effect of the treatment of the thyrotoxicosis upon the myasthenia gravis, one must take into consideration the tendency of both diseases to undergo spontaneous remissions and exacerbations. To be kept in mind also is the deleterious effect of prolonged, untreated thyrotoxicosis upon the economy of the body. We are impressed by the fact that the two cases in our series that were fatal had prolonged, uncontrolled thyrotoxicosis, with resultant emaciation and debility. In three of our five cases (cases 1, 3, 4), there were periods of control of hyperthyroidism with no apparent effect upon the myasthenia gravis.

With these considerations in mind, we suggest that all cases of the syndrome of myasthenia gravis and thyrotoxicosis be subjected to the most direct and definitive control of the thyrotoxicosis. When enough cases are thus treated, we may be in a better position to settle the controversy concerning therapy.

That the association of myasthenia gravis with thyrotoxicosis is not so rare as may be thought is borne out by Eaton's [22] statement that 6 per cent of patients with myasthenia gravis seen at the Mayo Clinic either have an associated hyperthyroidism or have had this disease before the onset of the myasthenia gravis. Further evidence as to the incidence of the association is the fact that we were personally able to observe four of the five cases in a general hospital in a period of one year.

Summary

Five cases of myasthenia gravis associated with Graves' disease are presented. Unequivocal response of the involved muscles to neostigmine and their sensitivity to curare are considered specific in differentiating myasthenia gravis from thyrotoxic myopathy. The controversy concerning

treatment of the associated thyrotoxicosis is discussed, and therapy of the thyrotoxicosis is recommended.

ACKNOWLEDGMENTS

We wish to thank Dr. Arthur A. Rodriquez, of the University of Illinois Physical Medicine Department, who performed the electromyography; Dr. D. E. Clark, of the University of Chicago, for the radioactive studies on case 1; Dr. Robert W. Keeton, head of Department of Medicine of the University of Illinois, for the use of case 4, and Dr. Louis K. Vorhaus, Resident in Medicine of the Research and Educational Hospital, for his cooperation in the work-up of case 4.

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RENAL ANOXIA SYNDROME: A REVIEW AND REPORT OF 22 CASES *

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Azotemia from nonrenal disease states has received much attention in the literature in recent years. Such azotemia has been described in a multitude of conditions— medical, surgical, obstetrical, physical and allergic. A variety of names has been given to this syndrome of renal insufficiency, among them acute Bright's disease, acute tubular nephritis, prerenal azotemia, lower nephron syndrome, traumatic kidney, shock kidney and crush syndrome. Since the pathogenesis and the pathologic lesions are equivocal and the only discernible common factor seems to be renal anoxia, we consider the best description to be *renal anoxia syndrome,* as suggested by Maegraith et al.[1]

It is improbable that azotemias produced by such diverse clinical entities are identical in etiology and pathogenesis. Moreover, descriptions of the lesions of the renal anoxia vary considerably. The pathogenesis also has been diversely ascribed to renal vasospasm from hormonal, toxic or neurogenic mechanisms, to nephrotoxins, to a reduction of renal blood flow by shunting mechanisms, and to nephron nephrosis.

It is the purpose of this paper to review the various clinical, pathogenetic and pathologic aspects of this interesting syndrome and to add our experience from our study of 22 cases obtained from the medical and surgical wards of the Cook County and Mount Sinai Hospitals of Chicago.

Clinical Aspects

The clinical appearance of the renal anoxia syndrome varies greatly with the etiology, pathogenesis, rate of onset and duration. If the onset of the causative factor is sudden and severe, such as occurs in crush injury or massive gastrointestinal hemorrhage, a full-blown picture of uremia may develop, including uremic frost, stupor and increased neuromuscular irritability. If the onset of the etiologic factor is more gradual, the symptoms of azotemia may be mild and insidious and include fatigue, anorexia and lassitude, e.g., the low salt syndrome induced by excessive mercurial diuretics and restriction of salt in treatment of congestive heart failure.[2] The urinary output also varies with the speed of onset and the pathogenesis. It varies

* Received for publication November 6, 1950.

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from the oliguria and anuria of shock to the adequate and even excessive urinary output of patients suffering from sodium depletion. Shock or prolonged hypotension, frequently described in the earlier reports, need not necessarily be present. Moreover, in some cases, moderate elevations of blood pressure have been reported.[3] Hemoconcentration appears to have been present in most cases in the literature. Excessive vomiting has been given as a cardinal symptom. The specific gravity of the urine has been reported over a wide range, and granular pigmented casts were frequently found together with varying degrees of proteinuria. Although twitching has been seen frequently, generalized convulsions are considered uncommon. The mortality rate has improved considerably since first reported as 90 per cent by Lucké.[4] This improvement in prognosis reflects our better understanding of the therapy of this condition.

Pathogenesis

It is evident that no one factor can be solely implicated in all cases of the renal anoxia syndrome. It appears that not all cases of the renal anoxia syndrome are the same pathogenetically, pathologically or even clinically. We hope that, with further study, classification into finer categories may be possible, and that improvement in treatment and prognosis will therefore result.

Many pathogenetic mechanisms have been described. The precipitation in the distal tubule of various types of casts (heme and others) with tubular obstruction has been suggested as a cause for the oliguria and the resultant nitrogenous retention.[5] However, the number of tubules so involved has been shown to be insufficient to produce the clinical picture. Furthermore, the precipitation of heme casts may be due to factors other than the mere presence of an excess of hemoglobin or myoglobin in the glomerular filtrate. According to Corcoran and Page,[6] oliguria and aciduria are prerequisite. Oliver [7] mentions a number of factors that influence protein precipitation in the distal convolution, viz., the isoelectric point of the protein, the pH of the tubular fluid, its electrolyte content, and the dispersive effect of urea. Hemoglobin and myoglobin and their degradation products have an intense vasoconstrictor effect and may thus enhance other mechanisms, to be discussed below. It should be mentioned that heme casts have been reported in this syndrome even in the absence of the destruction of blood or muscle.[8]

Several mechanisms of renal failure may be in effect in shock: (1) *Hypotension* decreases renal blood flow and effective filtration pressure. It has been shown that in shock the kidney circulation suffers more than the circulation of more vital organs, such as the brain and heart.[9] (2) *A renal vasoconstrictor* substance has been demonstrated by Corcoran and Page in the blood of animals and human subjects in shock.[6] (3) *Hemoconcentration* limits the amount of blood available for renal excretory functions, decreases renal blood flow, increases colloidal osmotic pressure in the capillaries of the

glomerulus, and increases the load of nitrogenous substances presented to the kidney for excretion owing to its effect in increasing protein catabolism.[4] (4) *Nephrotoxic substances* arising from injured tissues have also been implicated.[6] The exact nature of these substances has not been determined. Van Slyke,[9] as a result of his studies of kidney function in post-shock anuria, concluded that renal ischemia in traumatic shock and in the shock of dehydration produces organic changes in the tubule if prolonged. This results in azotemia, which is at first reversible but later becomes irreversible. In hemorrhage, in addition to anemic anoxia, many of the mechanisms implicated in shock are in effect. In gastrointestinal hemorrhage there is the additive effect of the digestion of large amounts of blood, the products of which a damaged kidney cannot excrete.

Trueta and his associates [10] have demonstrated a mechanism of *renal ischemia*. They observed that prolonged constriction of the hind leg of a rabbit produced severe vasospasm of the arteries supplying the cortex of the kidney, with a shunt through the juxtamedullary glomeruli. The arterioles of the juxtamedullary glomeruli are larger, contain fewer capillary loops, and have larger efferent arterioles, which break up into a coarse network to supply the tubules. These bear the major portion of the renal circulation. In some of these glomerular arterioles, the communication between the afferent and the efferent arterioles is, in a sense, no more than an arteriovenous connection, while the efferent arterioles enter almost directly into the veni recti. According to Trueta,[10] this by-passing of both glomerular filtration and the vessels of the tubule by branches from the glomerular efferent arteriole is sufficient to produce a decrease in the glomerular filtration and tubular damage. Trueta was able to produce the same result by stimulation of the splanchnic nerve. He demonstrated a remarkable increase in the rate of renal blood flow by the observation that the time required for the blood to traverse the kidney under these circumstances was cut in half, and that the renal veins showed red streaks and pulsations, indicating the presence of a more direct arterial communication. The reports of relief of the renal anoxia syndrome by splanchnic block[11] or by spinal anesthesia [12] may be clinical corroboration of Trueta's experimental observations.

Maxwell et al.,[13] however, have recently presented studies which seriously question the significance of the juxtamedullary shunt as a mechanism of renal insufficiency in man.

When *liver damage* is associated with azotemia, other factors are operative. In some cases, elevation of the non-protein-nitrogen may be due to a failure of deaminization and an increase in blood amino acid. However, blood amino acids are only infrequently elevated in disease of the liver, and then only in far advanced liver destruction. Nephrotoxic products resulting from a failure of the detoxifying function of the liver can be postulated, but evidence of their existence is meager.

Shorr [14] has brought out the effect of anoxia in the production of vasopressor and vasodilator substances from the kidney and liver, respectively. The effect of liver disease upon this delicate hepatorenal mechanism in the production of renal insufficiency remains to be determined.

The intimate relationship of the liver to salt and water metabolism may well be another factor.[15]

In cases of azotemia produced by *physicochemical alterations in the blood,* dehydration almost always is coexistent and produces manifold changes. With dehydration there is a remarkable increase in protein catabolism which may further tax the kidney. Extracellular dehydration is also usually associated with hypotension, increased viscosity of the blood, decreased renal blood flow and excess of potassium in the blood plasma. Lucké [8] emphasizes the importance of vomiting and resultant dehydration in his cases of lower nephron syndrome. The exact effect of disturbances of acid-base or individual electrolytes on renal function in the absence of dehydration still remains to be clarified. Acid metabolites, such as lactates and phosphates from injured tissue, may decrease the alkali reserve and thus augment acidosis and dehydration.

As previously mentioned, hyponatremia, as induced by frequent administration of mercurials with salt restriction in the treatment of heart failure and hypertension, has been incriminated as a frequent insidious cause of azotemia. Of the 21 cases of this syndrome reported by Schroeder,[2] 10 died before the cause for the azotemia was apparent. Eleven patients of this series recovered after proper administration of hypertonic saline solutions intravenously. No significant alteration in pH or CO_2 content is necessary for the production of this syndrome. Peters and Van Slyke [16] insist that the primary pathogenesis is one of dehydration. Characteristic renal lesions could not be demonstrated at autopsy in any of Schroeder's cases.

Transient local renal disturbances may also be concerned in the production of azotemia. There is evidence that the renal blood vessels can be influenced by psychogenic and neurogenic factors, as evidenced by hysterical polyuria, anuria and reflex anuria.[17] Reflex anuria from ureteral catheterization, reflex anuria from surgical manipulation distant from the kidney, and anuria in the normal kidney associated with a disease process in the other are well-known. Trueta [10] has demonstrated that splanchnic stimulation can produce cortical ischemia and renal insufficiency. This may be an explanation of the mechanism operative in the so-called idiopathic renal cortical necrosis.

Decreased renal function may also occur from venous congestion of the kidney in heart failure.[18] The impairment of function may be mild to moderate, but when this augments a decrease in function from other causes, a clinically significant azotemia is thereby produced. Evaluation and treatment of this factor in azotemia may prolong life in cardiovascular renal diseases.

Sulfonamides may produce azotemia by deposition of crystals in the ureter or pelvis of the kidney, with resultant hydronephrosis.[19] More often, the azotemia of a sulfonamide reaction is the result of the actual sensitization of the kidney to an antigen produced by the combination of the sulfonamide with kidney protein. In Lucké's cases the sulfonamides seemed to have played some rôle, inasmuch as they were used in the majority of cases reported by him.

Pathology

The pathologic changes in extrarenal azotemia have been variously described. It is evident that there is need for a finer classification of these azotemias on the basis of pathologic changes. The earliest descriptions were probably those of acute tubular parenchymatous nephritis, before the classification of Volhard and Fahr [20] led to the abandonment of this term. The pathologic features have been studied in various specific conditions, such as burns, shock, etc. Speaking generally, Moon [8] has described the pathologic features in extrarenal azotemia as follows: The kidneys grossly may be normal in size or moderately enlarged, usually soft, indicating edema. The capsule strips with unusual ease, the stellate veins and the cortical surfaces are engorged; the color varies, depending on relative degrees of congestion and of parenchymatous changes. Hemorrhagic streaks are seen in the medulla, and the cortical markings are frequently obscured. The microscopic picture usually shows hyperemia of the glomerular tufts and of the intertubular vessels. Capillary hemorrhages are sometimes present. Amorphous material is seen in the capsular spaces. The epithelium of the convoluted tubules shows acute degeneration, ranging to necrosis. *Usually these changes are more pronounced in the upper segments, sometimes in the lower; but, in general, all portions of the convoluted tubules are affected.* Plugs of debris often form in the lumens of the lower segments. The lumens may contain masses of deep red material when the cells containing it have disintegrated. Edema is a varying feature, more pronounced in the medullary than in the cortical zone.

Martineau and Hartman [21] show albuminous degeneration and simple necrosis in the *proximal* tubules of 18 out of 20 human cases of burns and in 66 out of 84 experimental burns in animals. They describe similar lesions in the *loop of Henle* in 14 out of 20 human cases and in 45 dogs. Bell and Knutson,[22] in a study of 84 cases in which the blood urea was elevated preterminally to uremic levels, showed that 20 of the 84 cases had mild to severe hydropic degeneration of the *proximal convoluted tubules,* while in the other 64 cases *no changes in the tubules* were demonstrable.

In the study of 47 patients with fatal thermal burns, Goodpastor et al.[23] report only 20 of the 47 patients with definite morphologic changes in the kidney at autopsy. In two of these patients the lesions were due to acute pyelonephritis, while the alterations in the other 18 were similar. In this group of 18 cases, degeneration and necrosis of renal tubules were found

in two sites: (1) *in the convoluted tubules,* and (2) *surrounding the casts lying within the distal portions of the tubules.* Tubular necrosis in the lower nephron, they found, was limited to the cells surrounding the casts. It is noteworthy that these authors do not mention special involvement of the distal convoluted tubules.

In a comprehensive article on extrarenal azotemia, Jeghers and Bakst [24] stated that changes in the renal tubules *are not specific,* and that the changes vary from microscopic degeneration to evidence of gross necrosis and, on occasion, are entirely absent.

Hashimoto,[25] by means of injections of histamine dichloride, has been able to produce a rise in non-protein-nitrogen, a fall of blood pressure, a markedly diminished urinary flow and a pathologic picture consisting of *diffuse degenerative changes in the tubular epithelium* with no changes in the glomeruli.

In 1946, Lucké [3] emphatically placed the lesions in the lower segments of the nephron, that is, in the thick loop of Henle and the distal convoluted tubules, and stated that there was relatively slight or no structural change in the upper parts of the nephrons, renal corpuscles, and proximal and intermediate segments of the tubule. However, an increase in glomerular permeability and some swelling of the epithelium of the capsule were also observed in his cases. Lucké also has found at times slight swelling and somewhat increased granularity of the tubular cells of the proximal segment.

As previously mentioned, Schroeder [2] found *no characteristic lesions* in the postmortem examination of the kidneys of patients dying of hyponatremia from treatment of heart failure.

French [26] has determined in 20 cases of extrarenal azotemia a *glomerular lesion* identical with that found in 10 of 11 cases of eclampsia which he studied. French also described changes in the tubules. *In the proximal tubule,* cloudy swelling was present, and in two instances it advanced to simple necrosis. He stated that *the most striking changes were present in the distal convoluted tubules,* as noted by Lucké [3] and Mallory.[27] Minor changes were present in all cases and were strikingly advanced in 16 instances. In these cases the most constant change in the distal convoluted tubules was the occurrence of dense, gray-blue stained casts, which were present in 19 of 20 cases.

In a pathologic study of 125 patients dying from heat stroke, Malamud et al.[28] described *ischemia* of the glomeruli, the presence of pigmented casts in the distal convoluted tubules and, in about one-ninth of their cases, *early degeneration of the cells of the distal convoluted tubules.*

Darmady,[29] in a series of six fatal traumatic cases in soldiers, describes the pathologic changes as occurring *mainly in the ascending limbs of Henle,* although the proximal convoluted tubules and the descending limbs were also affected. In the ascending limb of Henle and the distal convoluted tubule, the abnormalities were found in cells surrounding the hyalin casts. Other areas of degeneration were found in these positions without casts.

They found no obstruction in those nephrons containing casts. In a description of cases from 12 casualties who died in renal failure, Darmady [30] again described the abnormalities as occurring *mainly in the distal tubule.*

Maegraith [1] et al. describe the pathologic lesions as being concentrated chiefly in the *ascending loop of Henle and the distal convoluted tubules.* Odel [31] states that, in a histologic study of necropsies of acute renal failure, no morphologic explanation is adequate for the failure of urine formation. Hoffman and Marshall,[32] in their report, described in a fatal case of transfusion reaction *lower nephron nephrosis with renal edema* and *focal glomerulitis.* They reported that the glomeruli were normal for the most part, except for moderate thickening of the basement membrane, with the presence of polymorphonuclear leukocytes in some loops. The principal lesions were described in the lower nephrons, especially in the distal convoluted tubules. In many other reports, the site of the tubular damage is not specified.

In 12 postmortem reports concerning secondary shock, Herbut [33] describes the pathologic lesion as "severe degeneration to complete necrosis and even regeneration of the epithelial cells of the proximal convoluted tubules with relatively less degeneration of the distal convoluted tubules and still less or none at all of the lining cells of Henle's loops and the collecting tubules."

Bywaters,[34] in a discussion of the crush syndrome, states that the changes are largely in the proximal tubule. He considers that the alterations in the distal tubule are secondary to the precipitation of pigmented casts in that area.

Materials and Methods

An extensive search of the medical and surgical wards of the Cook County and Mount Sinai Hospitals was made for patients with conditions known to be associated with acute renal insufficiency. Cases of primary renal disease, such as nephritis, nephrosclerosis, congenital or destructive renal lesions and obstructive uropathy, were excluded. Thus, among the patients studied were those with severe infections, shock, hemorrhage, electrolyte imbalance, dehydration states, hepatitis, sulfonamide reactions, diabetic coma, cerebral hemorrhage, acute pancreatitis, hyponatremia as produced in the therapy of heart disease, gastrointestinal hemorrhage and fulminating ulcerative colitis.

In the screening of over 200 patients whose primary disease states might be etiologic in the production of acute renal insufficiency, 22 cases of this syndrome were revealed. These 22 patients were carefully studied from both the clinical and laboratory aspects throughout the course of the illness. Repeated determinations were made of the non-protein-nitrogen, blood urea nitrogen, creatinine, CO_2 combining power, serum chloride, hematocrit, urinalysis and blood phenols. Of these 22 cases, one-half survived. Autopsy examinations were performed in seven of the 12 fatal cases. Special attention was focused on the microscopic pathology of the renal tissue.

Case Reports of Seven Autopsied Patients

Case 1. A 44 year old white housewife entered Mount Sinai Hospital on February 17, 1949, complaining of sharp pain in the right upper quadrant radiating to the back, of several hours' duration. She had had one similar episode one year before, diagnosed as a "gall-bladder attack," which subsided on conservative treatment, and she had since lost 30 pounds by dieting. Physical examination on admission revealed an obese white female with blood pressure of 88 mm. Hg systolic and 50 mm. diastolic, temperature of 97.4° F., pulse of 80, and respirations of 24. A small lemon-sized tender mass was palpable in the right upper quadrant. Normal bowel sounds were audible. The following day the oral temperature rose to 105° F., tenderness in the right upper quadrant increased, and no bowel sounds could be auscultated. Several hours later, symptoms of shock were observed and the blood pressure was unobtainable. Complete anuria developed. One thousand cubic centimeters of blood were given and the blood pressure rose to 80/60. The patient's condition remained critical and fluids were limited to 1,000 c.c. per 24 hours. Only 20 c.c. of urine were voided. A transient pleuropericardial friction rub was noted on February 23. She appeared clinically improved, the blood pressure rose to 100/60, and 600 c.c. of urine were voided for the 24 hour period. However, she died suddenly one-half hour later. The pertinent blood chemistry data are recorded in the table. The blood amylase on February 18 was 1,625 units and on February 19 was 766 units.

Autopsy: Acute suppurative cholecystitis with cholelithiasis; ascending cholangitis; hepatitis and multiple small liver abscesses; acute fat necrosis of the pancreas with generalized retroperitoneal fat necrosis.

The kidneys were flabby and markedly enlarged, weighing 770 gm. together. The capsule stripped with ease, leaving a smooth, pale and glistening brownish surface. On cut section, the cortex was thickened and the architecture obscured. Fluid was oozing from the surface. Histologic study showed that most of the glomeruli appeared normal. The epithelial lining of the distal convoluted tubules was partially degenerated and a few cells had lost their nuclei. In some of these tubules the lumen was partly filled with desquamated and partly necrotic epithelial cells. Some of the tubules, both convoluted and collecting, were markedly dilated. Pinkish homogeneous casts were noted in some of these tubules. In the straight tubules the epithelial lining was degenerated in some areas; and in others, it showed evidence of regeneration in a few places. The tubules contained granular pinkish casts. There was edema of the interstitial connective tissue, which in some areas was infiltrated with plasma cells and lymphocytes.

Comment: The renal microscopic findings in this case coincide with the typical lower nephron nephrosis as described by Lucké. In this patient, both shock and severe toxemia were operative in the production of the renal damage.

Case 2. A 55 year old white female was admitted to Mount Sinai Hospital on May 20, 1949, in a state of acute congestive failure which had begun three days before with symptoms of acute pulmonary edema. She was known to have had rheumatic heart disease, mitral stenosis and moderate hypertension with repeated episodes of congestive failure during the past five years. Physical examination revealed a thin, acutely ill white female, sitting up in a semi-stuporous condition. The blood pressure was 178 mm. Hg systolic and 88 mm. diastolic. Auricular fibrillation with an apex rate of 96 was present. The respiratory rate was 26. Moist râles were audible over the right and left lower lung fields. The heart was markedly enlarged. A loud systolic murmur was audible at the apex. There was no edema. The patient did not

respond to the usual treatment of heart failure and became progressively more stuporous. Her urinary output for the first 24 hours was 30 c.c., and complete anuria ensued on the second day. She developed nuchal rigidity, and the spinal fluid was faintly xanthochromic. Transitory neurologic findings were noted, and she died on May 26 in what appeared to be a uremic state. Pertinent laboratory data are presented in the table.

Autopsy: Concentric hypertrophy of both cardiac ventricles; dilatation of the left auricle; marked fibroplastic stenosis and insufficiency of the mitral valve; chronic passive congestion and pulmonary edema with bronchopneumonia; large cerebral hemorrhage involving the right basal ganglia.

The kidneys weighed 360 gm. together. The capsule stripped with ease, leaving a smooth, slightly granular surface. Microscopic study of renal tissue showed most of the findings to be confined to the loops of Henle and the distal convoluted tubules, the glomerular structures and proximal convoluted tubules having minimal changes except for hyalinization of an occasional glomerular tuft. Many of the loops of Henle and the distal convoluted tubules were filled with granular pinkish casts. Some of this material resembled red blood cells. The lining epithelium in these areas was thinned and in some of them degenerated, or partly desquamated. Wherever the casts were present in greatest amount, the tubular damage was more severe, and the surrounding interstitial stroma was edematous and richly infiltrated with a mixture of eosinophils, lymphocytes, plasma cells, and phagocytic cells containing hemosiderin pigment. Also present in the stroma in such areas were particles of blackish-brown pigment. The small blood vessels were congested. Many collecting tubules contained large masses of pinkish granular material similar to the casts found in the distal convoluted tubules, but their epithelial lining was intact. In the pericapsular and peripelvic fibroadipose tissue, abundant plasma cell infiltrates were noted. The changes in the proximal part of the nephron were minimal, amounting to only slight congestion in the glomerular tufts and slight parenchymatous degeneration of an otherwise intact tubular epithelium.

Comment: The microscopic diagnosis was chronic interstitial nephritis, recurrent, with superimposed lower nephron nephrosis. Although this patient had a preëxisting chronic interstitial nephritis and a mild degree of nephrosclerosis associated with her longstanding hypertension, the dominant alteration in the kidney was the typical lower nephron nephrosis, including even the characteristic pigmented casts in the distal convolution. Despite the fact that during her hospital course the blood pressure and clinical picture was not one of shock, it is probable that the sudden massive cerebral hemorrhage produced a transient shocklike state that initiated the entire chain of events.

Case 3. A 41 year old white male was admitted to the Cook County Hospital on December 12, 1949, complaining of sudden onset of severe epigastric pain and continuous vomiting 26 hours prior to admission. He was known to have had an asymptomatic moderate hypertension for 10 years. Examination on admission showed him to be acutely ill and writhing with abdominal pain. Temperature was 104° F. Blood pressure and pulse were unobtainable for several hours. He was pale, sweated profusely, and appeared in a state of profound peripheral vascular collapse. His abdomen was distended, rigid throughout and silent. He was treated for shock with supportive measures, such as blood transfusions, plasma, morphine and antibiotics, but never rallied sufficiently for surgical intervention. Pertinent laboratory data are given in the chart. Serum amylase was 256 units. He was oliguric during the

TABLE I

Patient	History and Pertinent Physical Findings	Diagnosis	Date	NPN	BUN	Creat.	Hem.	Urine		Course
								Sp. Gr.	Casts P/H.P.F.	
(1) 42 yr. old C/M	Cong. fail. recurrent 3 yrs. Pul. edema, enlarged liver, pedal edema, systolic and diastolic aortic and mitral murmurs, BP 140/60, pulse 90.	Rheum. ht., aortic and mitral valvulitis, chronic recurrent cong. fail., salt depletion syndrome.	1/18/49 1/28/49 1/31/49 2/4/49 2/21/49	57 162 178 75 45	 104 139 55 28	1.7 9.0 7.5 2.1 1.8	 41 34 22 32	1.008 1.022 	few gr.	Azotemia produced by sodium depletion (Rx mercurials and sodium restriction) corrected by I.V. saline. Discharged as improved.
(2) 38 yr. old C/F	Known diabetic. Admitted in deep coma. Kussmaul resp., rate 12, markedly dehydrated. BP 130/80, T 102, pulse 110. 4+ sugar and acetone in urine.	Diabetic acidosis, severe, with coma and dehydration.	1/15/49 1/18/49 1/21/49 1/25/49	152 145 83 36	 120 65 22	7.2 6.8 3.1 1.4	 46 30 26	1.024 	0	Responded slowly to standard treatment. Diabetic acidosis. Sugar-free 1/20/49. Complete recovery.
(3) 46 yr. old C/M	Abdom. cramps, vomiting, intermittent obstipation and melena—2 weeks; marked dehydration. BP 146/78, pulse 108, x-ray abdom., small bowel obstructed.	Small bowel obstruction, cause undetermined. Dehydration from electrolyte imbalance.	1/26/49 1/27/49	93 43		2.2 2.0		1.028 1.022	0 0	Obstruction relieved spontaneously after gastric suction and I.V. fluids. Complete recovery.
(4) 26 yr. old W/F	Chronic alcoholism. Repeated DT's; continuous vomiting; semi-stuporous; dehydrated. BP 140/90, pulse 112, resp. 28. Liver 5 cm. below r.c.m. Plasma chlorides and sodium low. CO_2 97 vol. %. Metabolic alkalosis. Complete anuria 2 days.	Chronic alcoholism, Laennec's cir., alcoholic gastritis, metabolic alkalosis. Overtreated with isotonic saline and 0.6 M lactate to point of metabolic acidosis. CO_2 combining power on 2/7/49—27 vol. %.	2/5/49 2/7/49 2/15/49 2/28/49	93 107 64 36	 16	5.0 5.8 2.8 2.0	 30 21* 32	1.010 1.011 1.009 	0 0 0 	Electrolyte equil. eventually estab., azotemia corrected. Discharged in excellent condition.
(5) 25 yr. old C/M	Auto accident 2 hrs. prior to adm., crushing injury, multiple fractures, hip, femur and pelvis with urinary extravasation, prolonged shock, BP and pulse unobtainable; anuric 24 hrs., oliguric thereafter.	Multiple fractures, crush injury, true lower nephron nephrosis.	2/23/49 2/25/49 2/26/49 2/28/49	93 146 161 191	 102 122 	6.8 10.3 12.0 12.4	 35 35 40	 	 	Uremic frost—2/25/50. Died in uremic state 2/28/49. Autopsy not obtained. Coroner's examination—enlarged, swollen but grossly normal kidneys.

TABLE I—*Continued*

Patient	History and Pertinent Physical Findings	Diagnosis	Date	NPN	BUN	Creat.	Hem.	Urine		Course
								Sp. Gr.	Casts P/H.P.F.	
(6) 64 yr. old W/M	Suprapubic prostatectomy, obstructive uropathy, 1944. Acute bronchitis. Rx sulfadiazine 5 days prior to adm. Responded well and afebrile. Sudden anuria 2 days prior to adm. Twitching, irrational. BP 155/90, pulse 88, resp. 22, T 98. Sulfa crystalluria.	"Sulfa" nephrosis superimposed on old pyelonephritis, ascending.	3/14/49 3/19/49 3/21/49 3/28/49 4/27/49†	136 189 150 73 42	84 105 45 37	11.5 16.8 11.1 2.3 2.2	43 38 40 38 48	1.016 1.018 1.007	0 few gr. 0	Oliguria 300–600 c.c. daily, 4 or 5 days after adm. Fluids limited basic req. Less than 1,000 c.c. per 24 hours. Diuresis onset 3/22/49. Discharged recovered 4/1/49.
(7) 26 yr. old C/M	Acute respiratory infection. Rx "sulfa" unknown amount, prior to adm. T 103.6, P 130, BP 106/78. Px right up. lobe pneumonitis. Rx 14 gm. sulfadiazine; oliguria noted 3 days after adm. "Sulfa" stopped. Sulfa crystalluria.	Pneumonitis, severe, acute; "sulfa" nephrosis.	12/23/48 12/28/48 12/30/48 12/31/48	70 244 314 352	 282 	2.3 13.0 16.1 20.0		1.023 1.012	gr.4+ gr.4+	Complete anuria 24 hrs. 12/25/50. Oliguria 50–300 c.c. daily until death uremic state on 3/6/49. BP remained normal throughout.
(8) 63 yr. old W/M	Acute resp. infection. Rx 7.5 gm. "sulfa" and parenteral penicillin 1 week prior to adm. Good response. Rx. Afebrile, ambulatory until sudden peripheral vascular collapse day of adm. BP 110/90, P 100, T 99.4. EKG normal; no evid. myocardial infarction. No prev. hist. cardiovascular renal dis. T 105, P 130, resp. 38, râles both bases.	Peripheral vascular collapse probably due to "sulfa" reaction. "Sulfa" nephrosis.	3/18/48† 3/3/49 3/4/49 3/5/49 3/6/49	 273 272 276 313	9.2 205 220 	 11.5 7.4 7.4 8.1	 45 43 44 	 1.020 1.016 	 4+ 4+ 	Anuric and oliguric until death on 3/6/49. Fluids were limited to 1,000 c.c. daily. Sulfa crystalluria.
(9) 41 yr. old W/M	Sudden onset epigastric pain, vomiting sev. hrs. prior to adm. In profound shock with pulse and BP unobtainable, on adm. (See text.)	Acute hemorrhagic pancreatitis, prolonged shock, retroperitoneal fat necrosis, lower nephron nephrosis.	12/14/49 12/15/49 12/17/49 12/18/49	90 146 168 186	 96 132 157	7.0 8.6 11.0 12.3	 50 46 39	1.018	0	Died 6 days after adm. *Autopsy obtained.*

TABLE I—*Continued*

Patient	History and Pertinent Physical Findings	Diagnosis	Date	NPN	BUN	Creat.	Hem.	Urine		Course
								Sp. Gr.	Casts P/H.P.F.	
(10) 66 yr. old W/M	Weakness, abdom. pain, vomiting, bloody diarrhea 1 week prior to adm. Marked dehydration. BP 110/60, auri. fib.; appeared toxic and delirious. (See text.)	Acute fulminating ulcerative colitis, toxic hepatitis; azotemia secondary to dehydration and renal circulatory disturbance.	10/31/48 11/1/48 11/2/48 11/3/48	80 85 85 92		2.2 1.9 1.8 1.8		1.008 1.006	0 0	Progressively downward; died 4 days after adm. *Autopsy obtained;* see text.
(11) 69 yr. old W/M	Cough, dyspnea, chest pain 7 days prior to admission. Dehydrated, dyspneic, toxic and disoriented. T 103, P 120, R 36, BP 90/54. Coughing up thick purulent sputum. Râles, dullness, bronchial breath sounds rt. lower lobe. Sputum loaded with tubercle bacilli.	Pulmonary TB—far advanced. Azotemia probably due to dehydration and toxic nephrosis.	1/8/49 1/11/49 1/13/49 1/14/49	114 63 58 71	 37 38 46	2.3 1.4 1.7 2.0	 45 40 41	1.010	0	Progressive downward course. Died 1/18/49; autopsy not obtained.
(12) 27 yr. old C/M	Duodenal ulcer confirmed, x-ray —4 yrs. Sudden onset 3 hrs. prior to admission; abd. pain, hematemesis, melena. Mod. shock, sweating, P 150, R 32, BP 78/50, rigid silent abd., obliteration liver dullness.	Bleeding perforated duodenal ulcer; acute renal insufficiency. Lower nephron effect.	1/13/49 1/14/49 1/17/49	64 51 35	41 28 13	2.5 1.8 1.2	49 43 44	1.020	0	Laparotomy, purse-string suture to perforation. Uneventful recovery.
(13) 38 yr. old Mex./F	Chronic alcoholism. Recent 27 lb. wt. loss. Cont. hematemesis—24 hrs. prior to adm. Mild shock. BP 74/60, P 110, liver 4 cm. below r.c.m.	Chronic alcoholism, Laennec's cirrhosis; massive hemorrhage from esophageal varices. Lower nephron effect.	12/12/48 12/14/48 12/15/48 12/16/48 12/17/48 12/23/48	98 61 55 48 40 34	 39 28 28 22 18	7.4 3.0 2.2 1.8 1.4 1.2	 40 41 41 40 36	1.015	0	Blood transfusion, I.V. fluids. Complete recovery.

TABLE I—*Continued*

Patient	History and Pertinent Physical Findings	Diagnosis	Date	NPN	BUN	Creat.	Hem.	Urine		Course
								Sp. Gr.	Casts P/H.P.F.	
(14) 42 yr. old W/M	Chronic alcoholism—15 yrs. Dyspnea, orthopnea, cough, prog. edema, 3 wks.; BP 104/70, T 99.4, P 100, R 22. Rt. hydrothorax, râles left base, systolic, diastolic murmurs, aortic and mitral area. Liver 4 cm. below r.c.m.	Laennec's cirrhosis, acute hepatitis, superimposed. Chron. rheum. valvulitis, mitral and aortic valves. Azotemia from circulatory renal disturbances (cong. fail.), toxic hep. superimposed on mod. arteriolonephrosclerosis.	1/18/49 1/20/49 1/21/49 1/22/49	116 100 82 91	77 65 53	2.8 2.3 2.0 2.2	51 55 51 52	1.024	0	Jaundice noted 3 days after adm. Downward course, delirious, toxic. Liver profile hepatocellular damage. Died 1/22/49. *Autopsy obtained.*
(15) 69 yr. old C/F	Diabetic—3 yrs. Chills, fever, cough, vomiting. BP 104/78, T 102, P 96, R 20. Dullness and râles over rt. lower lobe. Painful swelling rt. leg. Mod. dehydration.	Diabetic acidosis; pneumonitis, thrombophleb., dehydration.	11/8/48 11/10/48 12/2/48 12/6/48	90 68 57 56	 39 35	4.0 3.8 2.3 2.3	 34 30	1.014	0	Rx diabetic acidosis, penicillin, "sulfa," Dicumarol. Recovered, discharg. residual mild azotemia.
(16) 41 yr. old C/F	Chills, fever, prostration, hemoptysis, several days prior to adm. T 99.8, P 110, R 32, BP 120/70. Toxic, dehydrated, disoriented, mild icterus; bilateral pulm. consolidation; enlarged liver.	Fulminating pneumonitis—bilateral. Etiology undeterm. Lung abscess, acute, rt. up. lobe. Chron. pyelonephritis with superimposed toxic nephrosis.	3/7/49 3/9/49 3/10/49 3/11/49	254 250 318 325	 253	15.0 8.6 8.6 7.8	 33 32	1.013	0	No response to supportive therapy and antibiotics. Died 3/12/49. *Autopsy obtained.*
(17) 57 yr. old C/M	Deaf mute. History unobt. BP 110/20, P 84 reg., R 20, T 98. Acute cong. failure. Blowing diastolic murmur Erb's point. Kahn 4+.	Luetic ht. dis., aortic insuff., card. failure. Azotemia prob. from renal circ. disturbance (cong. fail.).	1/3/49 1/5/49 1/7/49 1/8/49	70 88 117 210	 62 79 120	1.7 2.5 3.0 3.2	 34 34 34	1.003	0	No response digitalis, mercurials and salt restriction. Died 1/9/49; autopsy not obtained.
(18) 55 yr. old W/F	Rheum. ht. dis. 20 yrs. Recurrent cong. fail. 5 yrs. Acute cong. fail. 3 days prior to adm. Sudden collapse, shock, anuria. BP 177/88, P 96, irreg. Pulm. edema.	Rheum. ht. dis.—chronic; valvulitis. Cerebral hem., shock. Lower nephron nephrosis superimposed on chron. recurrent interstitial nephritis.	5/21/49 5/23/49 5/24/49	136 178 170	74 119 122	7.5 10.7 11.0		1.011 1.014	0 0	Became comatose, prog. worse; died 5/26/49; *autopsy obtained.*

TABLE 1—*Continued*

Patient	History and Pertinent Physical Findings	Diagnosis	Date	NPN	BUN	Creat.	Hem.	Urine		Course
								Sp. Gr.	Casts P/H.P.F.	
(19) 44 yr. old W/F	Known gall-bladder dis. 1 yr. Sudden onset rt. up. quad. pain, shock, anuria.	Acute suppurative cholecystitis, cholelithiasis, cholangitis, hepatitis, multiple sm. liver abscesses, acute fat necrosis—pancreas, gen. retroperitoneal fat necrosis. Lower nephron nephrosis.	2/18/49 2/19/49 2/21/49 2/23/49 2/24/49	40 71 177 188 217	13.9 37.6 69.5 166	 8.3 11.2 12.0	 40 35 37	1.022	0 0	Prog. azotemia. Fluids limited 1,000 c.c. daily. Died 2/25/49. *Autopsy obtained.*
(20) 23 yr. old W/F	Ingested half a glass home wave neutralizer (pot. bromate sol.) 48 hrs. prior to adm. Semistuporous on adm. BP 90/60, T 98.6, P 102.	Toxic nephrosis.	10/10/48 10/13/48 10/15/48 10/18/48 10/23/48	99 140 120 87 58		11.0 10.0 14.0 7.8 1.4				Complete anuria 7 days. 4–5,000 c.c. I.V. fluids daily. Edema and ascites noted; 5th day, anuria. Diuresis began 10/17/48. Complete recovery.
21) 68 yr. old W/M	Sudden onset chest pain, mod. shock; symptoms of cong. fail. and pul. edema, for 10 days prior to adm. BP 110/70.	Acute myocard. infarction, second. cong. failure. Azotemia from shock and disturbed ren. blood flow of cong. failure.	12/10/48	146		3.1		1.012	0	No response to card. régime; prog. downward course. Died 12/11/48. *Autopsy obtained.*
(22) 53 yr. old C/F	Known diabetic for many yrs. Careless about her diet. Adm. on 12/1/48 in diabetic coma. BP 140/94, R 32, P 100, T 97.6. Comatose, Kussmaul resp., markedly dehydrated.	Diabetic acidosis, coma, dehydration.	12/21/48 12/23/48	68 31	37 18	4.5 1.5	54 42	1.012 1.018	few gr.	Good response to usual treatment. Complete recovery.

* Transfusion of 1,000 c.c. of whole blood given.
† Determinations made as outpatient.

course of the illness, voiding only 100 to 400 c.c. per 24 hour period. He died in a uremic state on December 18, five days after onset of his symptoms.

Autopsy: Typical acute hemorrhagic pancreatitis with generalized retroperitoneal fat necrosis and peritonitis. The kidneys were large, flabby and pale, and weighed 600 gm. together. Study of the microscopic sections revealed that the capillary tufts of most of the glomeruli were markedly engorged. Bowman's spaces showed a pinkish stained precipitate of protein fluid. The epithelium of the proximal convoluted tubules was swollen, the epithelial cells were indistinctly outlined, the lumens of the convoluted tubules were open and contained, occasionally, deposits of eosinophilic granular material.

The distal convoluted tubules, tubules of Henle's loops and, occasionally, the collecting tubules contained brownish casts of a heme compound. The lining epithelium of these tubules showed degenerative changes, including frank necrosis. The interstitial connective tissue of the medulla was edematous, and the capillaries and veins appeared congested, especially in the corticomedullary junction. There was a focal—chiefly peritubular and perivenous—infiltration of leukocytes, lymphocytes, plasma cells and eosinophilic histiocytes in the medulla.

Comment: The pathologic changes in this case are predominantly in the distal convolution and loops of Henle and include the characteristic pigment casts. Again, the outstanding clinical feature was the prolonged shock producing lower nephron nephrosis.

Case 4. A 66 year old white male was admitted to the Cook County Hospital on October 31, 1948, with complaints of weakness, cramping abdominal pain and bloody diarrhea of one week's duration. Examination revealed him to be markedly dehydrated and extremely weak. Temperature was 102° F.

In spite of supportive measures, of antibiotics and blood transfusions, he died four days after admission. The autopsy findings were those of an acute ulcerative colitis and a toxic hepatitis.

Autopsy: The kidneys appeared grossly normal, and histologic study showed that the capillary loops were open. The lining epithelium of the proximal tubules showed some increased granularity, and the epithelial cells of the distal convoluted tubules were occasionally vacuolized. The lumens of the proximal and distal convoluted tubules contained acidophilic granular material.

Comment: The pathogenesis of the azotemia in this case appears to be dehydration, the toxemia of an acute ulcerative colitis, and hepatitis. At no time did this patient suffer from shock or oliguria. The pathologic alterations grossly and microscopically were minimal, and there was no microscopic evidence of lower nephron nephrosis.

Case 5. A 41 year old colored female was admitted to the Cook County Hospital on March 5, 1949, complaining of sudden onset, following a prolonged cold, of chills, fever, pain in the chest, anorexia and hemoptysis of one day's duration. She appeared acutely ill, toxic, dehydrated and delirious. The blood pressure was 120 mm. Hg systolic and 70 mm. diastolic, pulse 110, and respirations 32. The sclerae were moderately icteric. There were physical findings of bilaterai extensive pneumonitis confirmed by roentgenogram. The liver border was palpable 6 cm. below the right costal margin. In addition to pertinent laboratory data in the table, the Kahn and Wassermann reactions were both positive and a liver profile study indicated the presence of a severe hepatitis. Urinary output was adequate. Despite antibiotics

and supportive therapy, the patient's condition grew progressively worse and she died on March 12, eight days after the onset of her illness.

Autopsy: Extensive patchy pneumonitis of all lobes, severe toxic hepatitis and cardiac dilatation. There was no pathologic evidence of active syphilis. The right kidney weighed 160 gm. and the left 240 gm. They appeared enlarged but grossly normal. On histologic study the capillary tufts of the glomeruli appeared congested. The Bowman's capsule of some glomeruli and the arterioles (vasa afferentia) were moderately thickened. The convoluted tubules showed an increase in size and a marked increase in the granularity of the cells. The capillaries and the thin walled vessels of the medulla were markedly congested. The most striking features were the marked edema and the interstitial infiltration, streaks and clusters of inflammatory cells, polymorphonuclear leukocytes, lymphocytes, plasma cells, and occasional eosinophilic histiocytes.

Comment: In spite of the fact that this patient had, pathologically, inflammatory involvement of the interstitium of the kidney, we feel that the histologic findings were not sufficient to explain the severe azotemia. It seems likely that the pneumonitis, the toxic hepatitis and the cardiac dilatation played an extensive rôle physiologically in the precipitation of the azotemia because of the fact that histologic involvement of the kidney, tubules and glomeruli was comparatively minor. We suggest that this case falls into the classification of azotemia due to a toxic nephrosis, together with azotemia associated with toxic hepatitis.

Case 6. A 68 year old white male with a known history of hypertension was admitted to the Cook County Hospital on December 3, 1948, 10 days after onset of typical symptoms of an acute myocardial infarction with subsequent right and left ventricular failure. The duration and severity of the peripheral vascular collapse were not known. On admission he appeared acutely ill, dyspneic, orthopneic and cyanotic. There was a moderate dependent pitting edema. The blood pressure was 110 mm. Hg systolic and 70 mm. diastolic. The urinary output was satisfactory.

Autopsy: Large recent infarction of anterior myocardial wall; patchy pneumonitis of the left upper lobe. The kidneys were of normal weight and grossly showed minimal changes. On microscopic examination, a few fibrosed glomeruli were noted scattered throughout the cortex. The capillaries of the glomerular tuft were engorged with red cells. The epithelial cells of the proximal convoluted tubules showed an increased granularity and occasionally vacuolization. The epithelium of occasional distal convoluted tubules and Henle's loops were impregnated with basophilic masses of calcium and their lumens contained the same amorphous material. The interstitial tissue of the medulla was edematous and showed a few inflammatory cells, chiefly lymphocytes. The vasa afferentia were moderately thickened.

Comment: This case is another example of azotemia with only minimal kidney findings. The pathogenesis in this case seems to be azotemia following medical shock due to myocardial infarction. The added factor of heart failure with decreased renal blood flow was probably also operative.

Case 7. A 42 year old white male was admitted to the Cook County Hospital on January 15, 1949, with dyspnea, orthopnea and dependent edema of three weeks' duration. There was no history of hypertension, rheumatic fever, syphilis or renal disease. He had been a chronic alcoholic for the past 15 years. Examination on admission showed a blood pressure of 104 mm. Hg systolic and 70 mm. diastolic,

temperature of 99.4° F., pulse of 100, and respirations of 22. The heart was enlarged to the right and left and there were physical signs of a right hydrothorax. Systolic and diastolic murmurs were audible at the mitral and aortic areas. A mid-diastolic rumbling murmur was audible over the mitral area. The liver was palpable 4 cm. below the right costal margin. A moderate pedal edema was noted. The patient did not respond to the usual cardiac medication, and jaundice was noted on January 18. He became delirious and congestive failure was progressive. He died on January 22.

Autopsy: Advanced rheumatic valvular deformities involving both the aortic and mitral valves. Histologic study of the liver revealed a toxic hepatitis engrafted upon a chronic Laennec's cirrhosis. Microscopic findings in the kidney were as follows: A few hyalinized glomeruli were seen scattered throughout the cortex. The capillary tufts of the glomeruli were engorged and the spaces of Bowman's capsule contained pinkish-stained granular precipitate. The epithelial cells of the proximal convolutions were swollen and indistinctly outlined. The lumens contained frequent pinkish-stained precipitate. Some of the distal convoluted tubules and Henle's loops showed calcific deposits in the lumens and occasional calcific deposits in the epithelial cells of the lining. The capillaries of the medulla were markedly congested. The interstitial connective tissue about the hyalinized glomeruli showed frequent round cell infiltration. The vasa afferentia showed some thickening of the wall. The microscopic diagnosis was: (1) arteriolosclerotic nephrosclerosis, moderate; (2) passive congestion; (3) minimal calcification of renal tubules.

Comment: This is another case in which azotemia was present in spite of minimal renal pathologic findings. The azotemia in this case was probably due to a combination of the toxic hepatitis engrafted upon a Laennec's cirrhosis, and to heart failure producing circulatory changes in the kidney.

Results and Discussion

With such a seemingly endless field to choose from in as large a patient population as was at our command, it is noteworthy that a careful search for the syndrome has disclosed so few cases. Often the expected syndrome was not found when a known probable etiologic basis was present in a severe state. For example, a large percentage of patients with severe intestinal hemorrhage or with diabetic coma showed no evidence of nitrogenous retention. In other instances, however, azotemia was often unexpectedly present when the primary disease was relatively mild. A probable explanation may be that the renal anoxia is often superimposed on preëxistent subclinical renal injury. Such a conclusion may be further substantiated by the fact that some evidence of minor degrees of renal insufficiency persisted in many of our cases for a prolonged period.

The clinical picture [35, 36] in our cases has conformed to descriptions by previous authors. Some of our cases survived in spite of uremic pericarditis, muscular twitchings and even coma, findings which have been considered indicative of terminal uremia. The clinical picture was often obscured by the initiating disease. The degree of azotemia in our cases has not proved of prognostic value and did not parallel the severity of the primary condition.

As previously discussed, our cases also showed various pathogenetic mechanisms. It is important to determine whether all cases of acute renal insufficiency should be classified into medical and surgical renal anoxias. This concept has occurred to others, for Oliver [7] states that he is preparing a report dealing with the problem of ischemic damage and its relation to and differentiation from direct toxic action to the kidney.

It may be that in the group of cases without shock, normal kidneys may fail to excrete overwhelming amounts of protein metabolites which will, therefore, increase in concentration in the blood. Such a mechanism may be in effect in gastrointestinal hemorrhages without shock, in allergic conditions such as generalized atopic dermatitis, exfoliative dermatitis, or generalized urticaria, and in the absorption of large exudates or masses of necrotic tissue. In this same category of cases without shock but *with oliguria*, there may be insufficient water for excretion of nitrogenous products. Such circumstances may be operative in the severe dehydration of excessive vomiting, sweating, diarrhea, fever, acidosis, alkalosis and starvation. Dehydration may also be a significant extrarenal added insult in the uremia of primary renal disease.

Thus, it is apparent that azotemia from causes which are primarily nonrenal is of varied pathogenesis. At present, the cases reported in the literature appear to be insufficiently classified in relation to the pathogenesis of this syndrome. We would differentiate the azotemia of (1) delayed shock, i.e., lower nephron syndrome; (2) dehydration; (3) neurogenic and psychogenic anuria; (4) excess protein catabolism; (5) toxic nephroses; (6) the "hemoglobinuric kidney"; (7) the "allergic kidney" from agents such as sulfonamides, and (8) renal circulatory disturbances (as in heart failure). *It should be recognized that more than one etiologic mechanism is operative in most cases.*

From the pathologic lesions as described by many authors, and from the autopsy findings in our cases, *no constant pathologic pattern* is present in the renal anoxia syndrome. The pathologic changes range from no visible histologic change to severe degeneration of the cells of the tubules. There is far more physiologic and clinical than histologic evidence for involvement of the glomerulus. The general impression from a study of the literature is that the pathologic lesion varies with the precipitating cause of the acute renal failure. *In most cases in which a true lower nephron syndrome has been demonstrated histologically, shock appears to have been the dominant factor.* Because of the varied pathologic findings, a considerable controversy exists concerning the nature of *medical* and *surgical* shock. Our case *22*, in which *medical* shock occurred following coronary thrombosis, showed minimal renal changes, while most of our cases of *surgical* shock demonstrated a true lower nephron nephrosis. Where dehydration has been of prime importance, histologic examination of the kidney parenchyma has often revealed no demonstrable change. The prin-

cipal site of change is frequently limited to the cells surrounding pigmented casts, irrespective of the location of these casts. Both Goodpastor [22] and French [19] have stressed the degeneration of epithelium adjacent to casts. Casts are most commonly found in the lower nephron because ideal conditions for their formation exist in this segment. It may be that the conspicuous pathologic change depends upon the presence of these casts, whereas the precipitating mechanism may be elsewhere in the nephron. As shown by Oliver [7] and by Shorr,[14] the most metabolically active portion of the nephron is the proximal tubule. It is reasonable to suggest that the most active metabolic segment of the nephron would be the most sensitive to early anoxic damage.

In many instances, authors fail to mention the specific localization of the pathologic lesions within the nephron. Oliver [7] states that in pathologic conditions it is often difficult or impossible to differentiate histologically the various segments of the nephron. It is interesting that in the pathologic description of a single entity, such as the "burn kidney," variations in the location of the abnormalities from the upper to the lower nephron have been reported.

Summary

1. There has been a tendency to classify loosely all cases of acute renal insufficiency, as distinct from primary renal disease and obstructive uropathy, into the general category of the lower nephron syndrome, irrespective of the etiology or pathogenesis. It is our impression, from a careful review of the cases in the literature and our own experience during the past two years with 22 cases, including seven autopsies, that while the true lower nephron nephrosis as described by Lucké, Mallory and others most often is associated with shock or hemorrhage, other mechanisms causing the renal anoxia syndrome will not show a pathognomonic histologic pattern. For this reason, the term "lower nephron syndrome" is not appropriate in all cases of nonrenal azotemias.

2. A classification based upon pathogenesis is suggested.

3. The variable pathologic lesions of the renal anoxia syndrome are described.

Acknowledgment

The authors are indebted to Dr. Israel Davidsohn, pathologist, Mount Sinai Hospital, and to Dr. Paul Santo, of the Hektoen Institute of the Cook County Hospital, for the microscopic descriptions, and to Mrs. Adelaide Burke for her technical assistance.

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STUDIES IN DISORDERS OF MUSCLE. IV. THE CLINICAL MANIFESTATIONS AND INHERITANCE OF CHILDHOOD PROGRESSIVE MUSCULAR DYSTROPHY *

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Introduction

In the literature, childhood progressive muscular dystrophy has not been differentiated from other types of muscular disease and, in many cases, has been included with other forms of dystrophy in a common description, with the result that its clinical manifestations and its inheritance have been confused. We have pointed out previously [1, 2] that there are two easily identified groups of patients with progressive muscular dystrophy—the facioscapulohumeral and the childhood types—and that patients having a typical pattern of muscular atrophy fit well into one of these two groups with only an occasional exception.

We have already described in detail [3] the facioscapulohumeral type, as studied in one kindred. The presence of the childhood type in a large number of unrelated kindreds offered an unusual opportunity to study the trait in its various forms of expression and to obtain a clear picture of its inheritance. In the present communication, an effort has been made to give a comprehensive clinical description of the trait as observed in 33 different kindreds. Only a brief account of its inheritance is included here since a more detailed presentation is being made separately.[4]

Methods and Materials

The material of this report consists of 33 kindreds. In these families, 61 patients with childhood progressive muscular dystrophy were found. All living members of these kindreds thought to have neuromuscular disorders have been examined, as have the parents of our patients, their siblings and certain other genetically related individuals, even though these relatives were reported to be normal. In the study of these patients, special emphasis was placed upon examination for evidence of muscular atrophy, weakness or pseudohypertrophy, as well as on the creatine and creatinine metabolism in known asymptomatic carriers of the disorder. The general method was outlined in more detail in a previous paper.[3] Thirty-four of these 61 sub-

* Received for publication December 27, 1950.
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This study was supported in part by a grant from the United States Public Health Service.

jects with progressive muscular dystrophy of the childhood type have been studied in particular detail during the past three years while they were on the metabolic ward of the laboratory.

Clinical Characteristics of the Disease

The similarity of symptoms and signs among this entire group of patients makes it possible to describe them as a unit. In table 1 it will be seen that all of them are males between the ages of four and 29 years.

The age of onset of the disorder is very difficult to establish because of the extremely insidious character of the initial symptoms and signs. At birth and during the neonatal period, no evidence of muscular disability was noted in any of these children. In the great majority of these patients (table 1), the first symptoms and signs developed during the second, third or fourth years, and consisted of a waddling gait, inability to learn to run

Table I

Clinical Findings in Progressive Muscular Dystrophy of Childhood

	Born	Age in Years at Onset	Severity	Pseudo Hypertrophy	Comment
1	1946	3	+	+	Grade III heart murmur
2	1944	2	+	+	
3	1943	3	+	+	
4	1943	2	++	+	
5	1941	2	++	+	
6	1941	3	++	+	
7	1940	2	++	+	Poliomyelitis
8	1940	2	+	+	
9	1940	6	++	+	
10	1941	3	++	+	
11	1938	4	++	+	
12	1938	4	+++	+	
13	1938	3	++	+	
14	1937	2	+++	+	Colobomata of irides and retinae
15	1937	2	+++	+	
16	1937	2	+++	+	
17	1936	2	+	0	
18	1936	2	+++	+	
19	1935	3	+	0	
20	1935	7	++	+	
21	1935	7	+	+	
22	1934	3	+++	+	Congestive heart failure
23	1934	5	+++	0	Congenital heart disease
24	1933	2	+++	+	Arachnodactyly. Congenital heart disease
25	1932	3	+++		
26	1931	1	+++	+	
27	1930	5	+++	+	
28	1929	6	+++	+	
29	1928	6	+++	+	
30	1930	5	+++	+	
31	1928	2	+++	0	
32	1928	2	+++	+	Congestive heart failure
33	1927	1	++++	0	
34	1921	8	+++	±	

normally, or an evident tendency to fall more frequently than the average child. In only two cases was there any significant delay in sitting and walking, but both of these children walked before two years of age, although not in an entirely normal fashion. In three boys the parents noted the development of abnormally large calf muscles before any weakness was apparent. In two of these families a dystrophic child with pseudohypertrophy of calf muscles had been born previously, and the parents were therefore on the watch for the appearance of this anomaly.

The earliest signs found on physical examination were pseudohypertrophy of calf muscles and a peculiar waddling gait which was rather characteristic. Because of weakness in the pelvic and thigh musculature and in the sacrospinalis group, a certain degree of lordosis develops and the patient finds it necessary to swing his leg and body to the side on which he wishes to advance the foot.

The abdominal muscles and erector spinae group show some atrophy from the very beginning and contribute to the lordosis and abnormal gait described above. Progression in these muscle groups is somewhat less predictable, although the same insidious tendency to steady progression exists.

The deep pelvic musculature is actually the most severely affected at the onset of the disease and contributes the major fault leading to the abnormal gait. However, examination of these muscle groups was relatively difficult. Some estimation of their strength could be obtained by the use of the methods developed by orthopedists and physiotherapists [7] for the study of muscle involvement in poliomyelitis. The glutei, the quadriceps femoris and the hamstrings share the initial atrophy. The adductors usually show some preservation as compared to the other thigh muscle groups.

In the leg, a peculiar predilection for the tibial muscles was found. The peroneal muscles are also involved, and foot drop with dragging of the toes is another characteristic of the anomaly in gait. The calf muscles are preserved until the atrophy is well established elsewhere and only become severely weakened when all muscles are badly involved. The muscles of the foot are not involved until atrophy is marked elsewhere.

Gowers [10] described a sign which now bears his name and which is nearly always present at the time these patients first complain of weakness. It consists of a characteristic manner of arising from the prone or supine position. The children roll onto their abdomen and raise their pelvic girdle by walking forward with their hands on the floor. The trunk is then brought to the erect position by pushing with the hands on the ankles, knees and thighs. Such a maneuver is necessary because of the weakness of the pelvic and erector spinae muscles. Other patients with muscular weakness of similar distribution also show the sign, as do certain patients with generalized debility or ataxias, particularly those due to cerebellar defects. Thus, although it is a consistent sign in childhood dystrophy, it is not a critical differential diagnostic point in recognizing the disorder among the diseases which are most often confused with it.

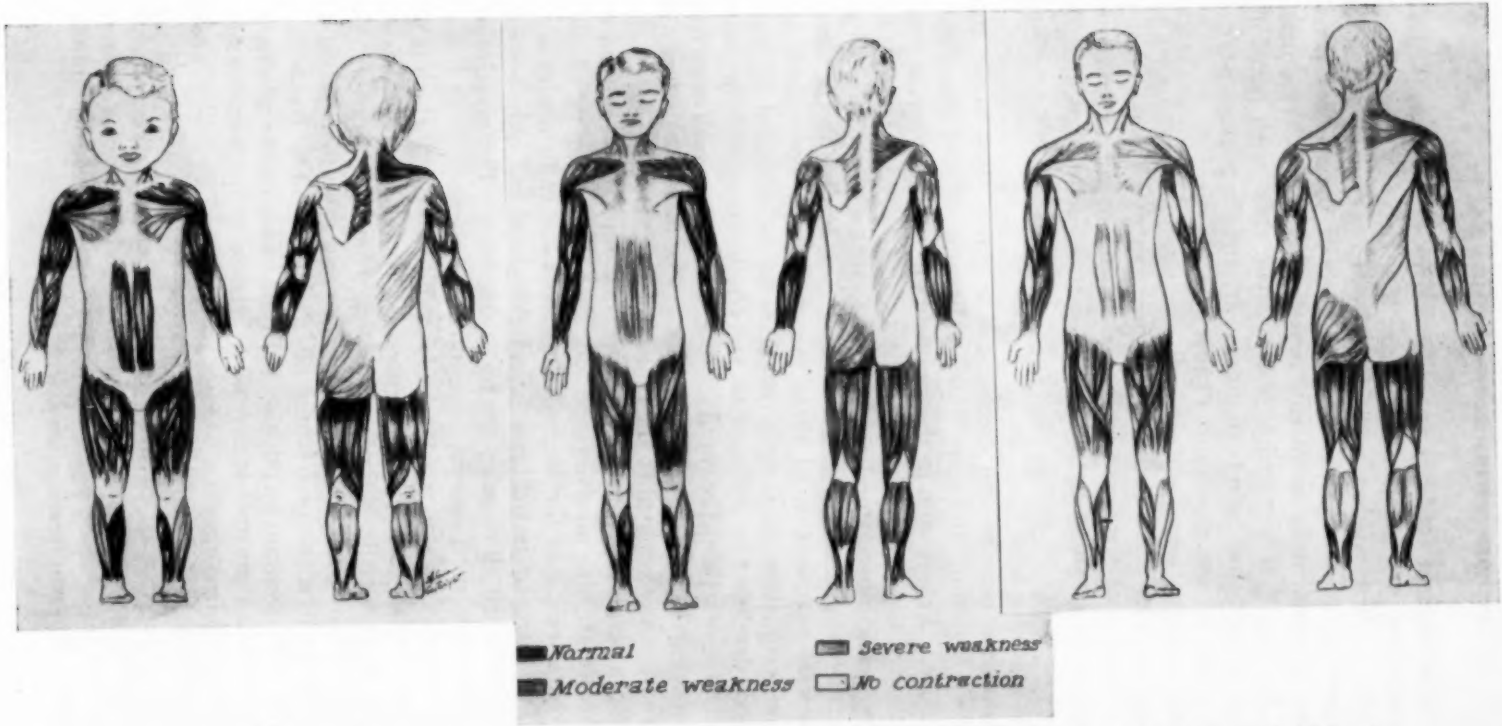

FIG. 1. Semi-diagrammatic representation of the pattern of muscular atrophy at three stages in the development of childhood progressive muscular dystrophy.

The pectoral girdle muscles are involved relatively early, although this occurs after the initial changes take place in the pelvic girdle. The first changes in the pectoral girdle consist of atrophy of the sternal head of the pectoralis major, the lower fibers of the trapezius, and the upper part of the deltoid (figures 3 and 4). Subsequently, the process begins in the other scapular muscles. The progression of the atrophy occurs insidiously, continuously, symmetrically and concurrently in the entire group. The biceps and triceps brachii are involved relatively early. The muscles of the forearm are preserved, with the exception of the brachioradialis, until the remainder of the process is very evident. The intrinsic muscles of the hand are the last to be seriously involved.

TABLE II

Muscle	Pattern of Muscular Involvement in Childhood Progressive Muscular Dystrophy			
	Early	Advanced	Far Advanced	Occurrence of Pseudohypertrophy
Facial, except zygomaticus	0	0	0	0
Zygomaticus	0	2	2	0
Pectoralis major,				
sternal head	1	4	4	0
clavicular head	0	1	3	0
Deltoid	0	2	3	Occasional
Triceps	0	2	4	Rare
Biceps	0	2	4	0
Brachioradialis	1	3	4	0
Trapezius, upper fibers	0	1	3	0
middle and lower fibers	2	4	4	0
Latissimus	1	3	4	0
Abdominal	0	2	3	0
Glutei	2	3	3	Rare
Tibials	2	4	4	0
Peroneals	1	3	4	0
Calf group	0	1	3	Usual but not constant
Intrinsic of hands	0	0	2	0

0 No change
1 Significant weakness
2 Moderate weakness
3 Severe disability
4 No contraction detectable

The facial muscles are almost completely spared except for the zygomaticus, the loss of which results in a transverse smile. Occasionally the orbicularis oris is mildly atrophic, with a tendency to pouting of the lips, but the characteristic changes of facioscapulohumeral dystrophy do not occur and the facial involvement is not progressive. Completely incapacitated children were able to whistle and make nearly all facial movements normally (figure 2). The muscles of mastication and swallowing are not involved. The cervical muscles are, in general, spared until late in the disease.

FIG. 2. Normal puckering in a patient with severe childhood dystrophy at age 13. Compare with the severe muscular atrophy shown in figure 7 of the same patient.

FIG. 3. Initial atrophy in lower fibers of the trapezius in an 8 year old boy. Note that the other scapular muscles are relatively intact except the proximal portion of the deltoid.

The best diagnostic criterion of the disease is the characteristic pattern of muscular atrophy which develops as the disorder becomes more advanced (figure 1). Table 2 presents the relative rate of atrophy in diagnostically useful muscle groups. Figures 5, 6 and 7 show various stages in the progression of the disorder.

Although minor differences can frequently be discovered between the same muscle on the right and left, there is a remarkable symmetry of the process when the extent of deviation from normal is considered. In the absence of some symmetry, it can be assumed that the disorder is not progressive muscular dystrophy in the specific sense in which that term is used here. The majority of patients with such asymmetric involvement have

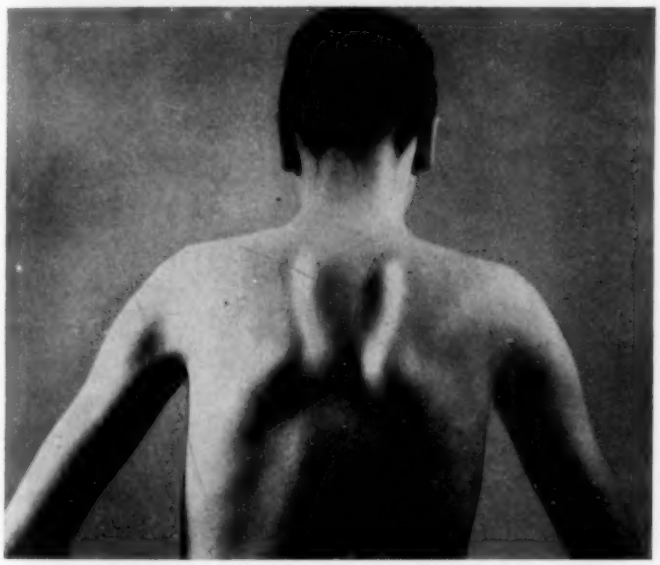

FIG. 4. Moderately advanced atrophy of the scapular muscles, particularly the rhomboids and trapezii, of a 15 year old patient.

had poliomyelitis or peripheral neuritis. They also run a very different course and give a history of an acute episode followed by definite improvement.

Pseudohypertrophy has received a great deal of emphasis in previous descriptions of this disease. In progressive muscular dystrophy it consists of fatty and fibrous replacement of muscular tissue, which takes place in such manner that the muscle enlarges at the same time that it becomes weaker. Many but not all of the patients described here had pseudohypertrophy (table 1). In the majority of cases the pseudohypertrophy was limited to the calf muscles, although a few patients also showed enlargement of other muscles, particularly those of the scapular group, most commonly

the triceps and deltoids. The muscles which were enlarged did not subsequently become extremely small, and some strength persisted in them throughout life, in contrast to the extreme atrophy and weakness of the muscles manifesting only atrophy. The phenomenon of pseudohypertrophy in this same group of patients and in certain others has been discussed in detail elsewhere.[2]

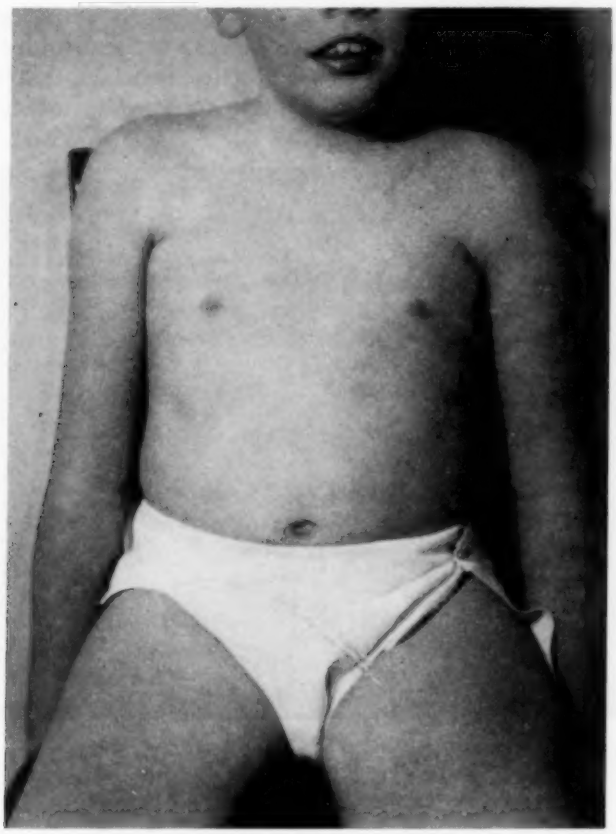

FIG. 5. This patient shows the characteristic pectoral girdle atrophy of the moderately advanced disease.

The clinical course of the majority of these patients has been a consistent one, as shown in table 1. Typically, after the onset in early childhood, these patients walked with slowly increasing difficulty until nine to 12 years of age, when they became confined to a wheelchair because of inability to walk without support. In addition to the muscular weakness, they developed contractures in the Achilles, hamstring and biceps tendons which contributed to their disability. The contractures were in some degree postponed by persistent activity and/or physiotherapy. Without the most persistent care,

the boys became progressively deformed once they were unable to walk, until grotesque deformities were present in the position which the child elected or had to use because of his weakness. Marked kyphoscoliosis frequently developed. The patients seldom survived beyond the age of 25 years. The majority died as a result of intercurrent respiratory infections. None of these boys has developed primary respiratory insufficiency. When the atrophy became very severe the cough sometimes lacked strength; in all probability this contributed to their susceptibility to pulmonary infection. Many of these boys also developed depression of the sternum (pectus excavatum) in adolescence.

FIG. 6. Well established progressive muscular dystrophy. Note the pectoral girdle atrophy, upper arm and thigh changes and enlargement of calf muscles associated with foot drop and inversion of the feet.

In general the progression has been so extremely insidious that neither the patient nor his parents could give any details except those relating to major catastrophies, such as the date at which ambulation became impossible. In reviewing the material, one gains the impression that after puberty the rate of progression is definitely slower. In those individuals who have survived to the age of 20, the rate of change has become extremely slow.

Because of the severe disability which nearly always develops before maturity, reproduction does not occur. None of these patients was mar-

ried. Furthermore, we do not know of any authentic reports of offspring of childhood dystrophics. However, such individuals as numbers 21 and 13 (table 1), who have reached adolescence without severe disability, might conceivably have children at some future time. Their progress will be watched with interest, in particular with the object of determining whether the reports of postpubertal remissions which are to be found in the old literature [9] can be confirmed.

All of these children had a persistent tachycardia of 100 to 120 beats per minute with a normal sinus rhythm. In addition, two had suffered epi-

FIG. 7. Extremely severe muscle atrophy in a completely incapacitated patient with childhood progressive muscular dystrophy.

sodes characteristic of congestive heart failure, one of which had been relieved by digitalis medication and salt restriction. At present, both patients are able to carry on a bed-and-wheelchair existence without medication and without any evidence suggestive of cardiac disease or congestive failure except sinus tachycardia. It should be emphasized that these patients lead a basal existence and that no satisfactory test of cardiac reserve has been devised for them. Thus their lack of clinical symptoms or signs of heart failure does not necessarily mean that their hearts are normal. Electrocardiographic tracings have been obtained and show one or more significant

abnormalities in most cases. They will be reported separately, together with data dealing with the heart in other types of dystrophy.

Another finding which has been present consistently is a peculiar change in the skin and subcutaneous tissue. The skin, particularly of the legs, was frequently mottled, even in an ambient temperature, and tended to be smooth and soft. The subcutaneous tissue felt less elastic than is normally found. This, together with the contractures and the reduced size of the subcutaneous veins, made venipuncture a difficult problem in many of the patients. An unusual change in the long bones has been described [8] and was observed in some of these patients.[6] The shafts of these bones were extremely small, with narrowed cortices and rarefaction of the heads which were, however, of approximately normal size. These two observations suggest that bone and subcutaneous tissue as well as muscle are involved in the anomaly of progressive muscular dystrophy.

In this series only a few associated congenital anomalies were observed. Three of the patients had evidence on physical and roentgen-ray examination suggestive of the presence of interatrial or interventricular septal defects in their hearts. One patient (case 14, table 1) had bilateral colobomata of the iris and retina. His brother (case 7, table 1) previously reported in detail,[2] had had acute anterior poliomyelitis affecting his right leg after the onset of his dystrophy. Minor infections and the exanthems of childhood did not appear to be unusually frequent in our series of cases.

There was little evidence that any other primary disease process was associated with the muscular disorder.[5] Neurologic examination revealed no abnormalities. The white cell and differential counts were normal and there was no anemia. The urine and stools were consistently normal. Except for the presence of creatinuria and reduction of urinary creatinine, more or less in proportion to the severity of the process, no metabolic abnormality was evident. Serum creatinine values were reduced and serum creatine values elevated. Details of the studies on the nature of the creatine-creatinine anomaly in this disease will be reported separately.[6]

Inheritance of the Disorder

The 33 kindreds have been divided for convenience of analysis into three groups (table 3). The first group consists of seven kindreds in which a clear-cut, sex-linked recessive pattern of inheritance is evident. Figure 8 is an example of such a kindred. In these lines the disorder occurs only in males and is transmitted only by females. Of the 58 male children of the direct carrier line females, 31 have had the characteristic clinical manifestations of the trait. Such data leave little doubt that the inheritance is that of a sex-linked recessive mechanism.

There are 14 kindreds in group 2 on whom the data were not sufficient to determine precisely whether the trait had been passed through a line of carrier females.

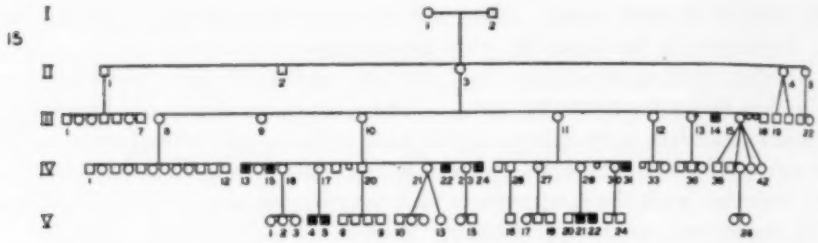

FIG. 8. Characteristic example of the sex-linked recessive inheritance found in the kindreds classified in group 1.

Group 3 consists of 12 kindreds in whom apparently isolated cases have occurred and in whom the number of known normal male children of the direct line of female progenitors was seven or more. Figure 9 is an illustration of one of these kindreds. These findings are incompatible with the concept that the trait has been passed through a line of female carriers, and suggest that new mutations have occurred. Confirmation of this is found in kindred 31, where identical twin boys developed the trait but seven other children in the same family were normal.

By comparing the number of cases in group 3, born locally, with the total birth rate for the area during the decade from 1930 to 1940, it has been possible to calculate a minimum mutation rate of approximately 1.0×10^{-4}.[4] This rate is one of the highest reported for a human gene.

Actually, the persistence of this disease as one of the relatively common neuromuscular anomalies from the time of Gower [10] to the present also supports the hypothesis of a frequent mutation rate. Since the trait occurs only in males and they never reproduce, it would rapidly disappear by selection if other cases were not supplied by new mutations. In such traits, the expected ratio in the tenth generation from a carrier female would be

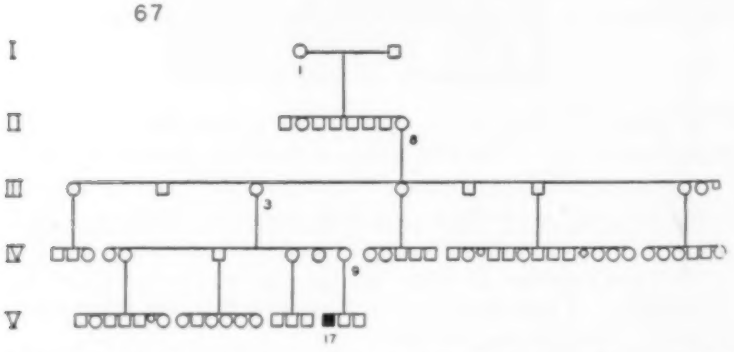

FIG. 9. Apparently isolated case of childhood progressive muscular dystrophy in which the number of normal male descendants of the female line (12 in this kindred) essentially excludes the possibility of transmission of a sex-linked recessive and suggests a new mutation.

TABLE III

Summary of Data

Group I

Number in a Direct Line from First Female

Kindred Number	Females	Normal Males	Affected Males
11	19	6	6
15	18	8	10
53	9	6	4
54	2	1	2
124	12	6	5
125+	4?+	0?+	4+
Total 6	66	27	31
Group II			
13	9	6	1
30	8	3	1
43	9	6	1
44	8	4	1
56	7	0	1
59	9	5	1
64	10	5	1
68	11	6	2
83	14	5	1
89	0	0	1
92	13	14	3
126	3	5	1
127	10	6	1
132	3	5	1
Total 14	114	70	17
Group III Number in a Direct Line from First Female			
7	9	7	1
12	7	8	1
14	10	7	1
24	13	10	1
26	8	11	1
31	7	9	2*
36	15	9	1
37	12	10	1
67	12	12	1
91	10	7	1
120	15	11	1
128	13	9	1
Total 12	131	110	13
Grand Total 33	311	207	61

+ Not used in calculations because the sex of the normal sibs in one family was unknown
* Identical twins.

1,023 normal females, one carrier female, 1,023 normal males and one dystrophic male. In many kindreds the presence of a single case can be explained only on the basis of a new mutation or some unknown environmental factor. The latter seems highly improbable because of the similarity

of the apparently sporadic cases to those of group 1, in which a definite pattern of inheritance is evident.

In the light of the evidence available, the trait seems to be the result of a sex-linked recessive gene which appears frequently in the population by mutation.

Differential Diagnosis of Muscular Dystrophy, Muscular Atrophies and the Ataxias

Using the characteristic pattern of muscular atrophy as the main clinical criterion, we have experienced little difficulty in identifying the cases which fit into the pattern of disease which we have called childhood progressive muscular dystrophy. As has been recorded previously,[1] the entire group is similar in age of onset, in muscles initially involved, in order of progression of the muscular atrophy and in sex, and have a pattern of inheritance consistent with a sex-linked recessive trait. Neurologic findings are consistently absent. The gait is somewhat similar to that of children with ataxias due to cerebellar or corticospinal tract abnormalities, and care has to be taken to differentiate the two groups of patients. The presence of weakness of individual muscle groups in dystrophy and of other signs of the neurologic disorder in the ataxias usually makes the decision easy. Table 4

Table IV

Comparison of Symptoms and Signs of Several Neuromuscular Disorders

Disease	Age of Onset	Initial Area of Muscular Atrophy	Rate of Progress	Survival	Inheritance	Neurologic Findings	
						Motor	Sensory
Progressive Muscular Dystrophy Childhood Type	2–5 years	Proximal in pelvic girdle	Rapid	Usually not beyond young adult	Sex-linked recessive	None	None
Facioscapulo-humeral Type	10–17 years	Proximal in pectoral girdle	Slow	Normal	Dominant	None	None
? Other Types	Variable	Similar to above	Variable	Variable	?	None	None
Ataxias (Friedreich's, Marie's, etc.)	8–15 years	None or distal in extremities	Moderately rapid	Variable, usually not beyond young adult	? Dominant	Pyramidal and/or cerebellar tract loss (pes cavus)	Posterior column loss
Peroneal Muscular Atrophy	10–20 years	Distal in extremities	Slow	Normal	Dominant	Occ. pyramidal rarely cerebellar tract loss, fasciculation	Usually peripheral nerve pattern of loss
Infantile Muscular Atrophy	First 12 months	Usually in extremities or none identifiable	Very rapid	Variable. Frequently only a few months	Hereditary but no definite pattern established	None	None

will serve to emphasize the contrast between childhood progressive muscular dystrophy and the various diseases which are frequently confused with this disorder.

This brief summary of the main points in the differential diagnosis of the hereditary neuromuscular disorders is not meant to be a completely adequate basis for the differential diagnosis of all the related neurologic disorders but will, we hope, serve to emphasize certain points. A few words of explanation of certain categories are needed. In addition to the two easily recognized types of muscular dystrophy which we have described, certain cases and groups of cases within a family occur which seem to be related in terms of clinical course and pattern of muscular atrophy to the dystrophies, and yet do not conform in all details to the common syndromes. Our category of "other types" under the heading of progressive muscular dystrophy is intended to point out this fact, although it is a miscellaneous group the need for which only serves to emphasize the incompleteness of our present understanding of the pathogenesis of progressive muscular dystrophy.

With such a tabular presentation as this, the similarity between the hereditary ataxias and peroneal muscular atrophy becomes apparent. This relationship has been an impressive one in our experience. Certain kindreds have shown signs in which features of both syndromes were present. Indeed, it might be well to think of these disorders as a spectrum of diseases in which any one, part, or all of a group of neurologic lesions may be genetically determined but become manifest only at certain developmental levels after birth. Probably each syndrome results from a separate mutation either of the same or of a different gene.

Discussion

The consistent clinical pattern and the clear-cut type of inheritance which we have observed in this group of patients are in contrast to the reported experience in the literature as summarized by Bell,[11] who found many types of the disease as well as pedigrees consistent with several different kinds of inheritance. Unfortunately, she had to depend upon published reports and hospital records which represented a heterogeneous collection of cases studied by physicians with greatly varying degrees of familiarity with neuromuscular disorders.

The opportunity to examine a large number of affected as well as normal members of 33 kindreds has made it possible for us to gain a picture of the various manifestations of a single disease and to derive a simple conclusion concerning its inheritance.

The evidence indicates that all of the cases are the result of an identical mutation which occurs frequently in a sex-linked gene and is uniformly recessive. Among the practical implications of this study is the opportunity which it affords the physician to give the parents of dystrophic children sound advice concerning their risk of having other dystrophic children. A

carrier female will transmit the trait on the average to one-half of her sons. The defective gene will also pass to one-half of her daughters, who will be carriers. Normal males will not transmit the gene. In sporadic cases which are apparently due to new mutations it is seldom possible to determine where the mutation actually occurred. Unless there is good evidence to the contrary, it should be postulated that the mother of a dystrophic son is a carrier of the abnormal gene, and eugenic advice to parents should be based on that presumption.

On the other hand, obliteration of such traits as this one appears to be, cannot be expected even with complete eugenic control because of the frequency with which the mutant occurs. Nonetheless, the prevention of the social disaster of multiple incapacitated children in a single family is a worthwhile accomplishment.

Conclusions

1. A summary is presented of a detailed clinical study of 34 patients with childhood progressive muscular dystrophy.

2. The clinical findings become apparent in the first few years of life, and a characteristic and symmetrical pattern of muscular atrophy develops in childhood. The large pelvic girdle muscles are the first involved in a process which spreads centrifugally in an insidious fashion to produce extreme muscular disability. Most of the patients are severely disabled in adolescence and die then or in early adult life. None of these patients has had children.

3. Among 33 kindreds in which 61 cases of the disorder are known to have occurred, the data are consistent with the interpretation that it is inherited as a sex-linked recessive trait, but with a mutation rate of approximately 1.0×10^{-4}. This high mutation rate accounts for the many apparently sporadic cases of childhood progressive muscular dystrophy.

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ATYPICAL FACIAL NEURALGIA IN THE HYPOTHYROID STATE*

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A deficiency of the thyroid hormone in the adult may give rise to a syndrome of chronic, recurring pain about the face and neck and recurring headaches, as recently pointed out by Fenichel.[1] The type and intensity of the pain vary considerably, and may be manifested as a dull aching or throbbing pain in either carotid area, in or about the ear, in the frontal or temporal area, or along the upper or lower jaw or the posterior cervical area. Quite frequently there may be an associated dull pain or sense of constriction over the precordium. The pain may be quite intense or merely a dull ache, but it is annoying because of its chronicity. When a patient complains of this type of facial pain, has recurrent and at times persistent headaches, is subject to fatigue and insomnia and is inclined to be sensitive to cold, the existence of the hypothyroid state is likely. This sequence of events has not been given enough emphasis. Too many patients with vague pain in the facial areas have been dismissed after proper nose and throat examinations and dental roentgenograms were pronounced negative, and have been informed merely that the diagnostic procedures revealed no evidence of disease.

As pointed out by Grollman,[2] "The early stages of thyroid deficiency are often marked by subjective nervousness, poor emotional control, irritability and mental depression which are often mistaken for neurasthenia." These patients are introspective, and recurrent facial neuralgia or headaches or, frequently, precordial pain contribute to their depression and anxiety.

Many types of pain are encountered in hypothyroidism. Grollman[2] mentions vague pain in the occipitocervical area of the head, rheumatoid pains in the joints and muscles, and vague pains in the abdomen, the latter often mistaken for appendicitis, gall-bladder disease or renal lithiasis. Seward,[3] in a study of mild cases of hypothyroidism, mentions one case with precordial pain with radiation into the left shoulder and arm accompanied by a sensation of a "heavy weight on the chest" severe enough to require morphine on two occasions. He also mentions dull aching pains in the lower abdomen and hypochondrium and, more frequently, headaches, usually in the vertex and radiating into the suboccipital region, as well as vague pains in the muscles and joints.

Aside from the occipitocervical distribution of pain, little attention has been paid to recurring pain about the face, which is suggestive of the old type of Sluder's neuralgia, a syndrome often questioned by neurologists and neurosurgeons. Wechsler[4] summarizes the findings in Sluder's neuralgia

* Received for publication January 16, 1950.

or neuralgia of the sphenopalatine ganglion as follows: "From among the atypical cases of trigeminal neuralgia which do not yield to surgical or other treatment, Sluder isolated a small group of neuralgias of the sphenopalatine ganglion. The pain in those instances is not along the course of the trigeminal divisions, but is diffuse behind the root of the nose, in the eyes, over the side of the face and cheek bone; it often radiates to the back of the head and down the occiput to the back of the neck and occasionally to the shoulders or even lower." He adds that some atypical neuralgias may be psychogenic in nature.

Gittens [5] believed that periodic headaches and facial neuralgia in the ordinary ambulatory office patient were on a vasomotor basis of hereditary origin, and further characterized by transient upsets in physiology, local tissue or fluid reactions in the brain, meninges, ganglions and nerve sheaths, with no real pathologic lesions which can be proved by physical examination, roentgen or laboratory studies, operation or postmortem findings.

Many of these cases fall into the hypothyroid group. The pain may be the result of deficient oxygenation or cell metabolism in the tissues as a result of the secretion of insufficient amounts of thyroxine or circulating thyroid hormone. In many respects it is similar to the aching type of pain manifested by many people when the barometric pressure is low. These cases seemingly are not related to the histamine cephalalgias, in which the anaphylactic response produces the unilateral headache around the frontal and temporal areas. In the hypothyroid or hypometabolism group there is no consistent localization, and the aching or pain may occur simultaneously in several widely separated locations. Since there are no tissue sections available for pathologic examination, it is a matter of speculation as to whether there are actually early atrophic changes in the thyroid or whether it is merely temporarily depressed, as in certain seasons of the year.

The determination of the basal metabolic rate in itself is admittedly only a rough index in the determination of the hypothyroid state, but it is of value when used in conjunction with careful clinical examination and history taking. Cholesterol determinations were inconclusive and were omitted in the tabulation of our cases. A study of protein-bound blood iodide was not available. However, in the following summary of 29 cases which are classified in the hypothyroid group as a result of a low basal metabolic rate as well as suggestive clinical histories, it will be noted that pain in the face or neck was either the presenting complaint or was mentioned as one of the prominent symptoms. In this group there are 25 women, averaging 34.8 years of age. The four males are somewhat older, two being 58 and 59, respectively, while the others were 43 and 35 years of age. This may be of significance, as the complaint of facial neuralgia occurred at a much younger age in the females, 10 being in the second decade, seven in the third decade, seven in the fourth and only one in the fifth.

The pain is not intense, as in true trigeminal neuralgia, but it is annoying

and aggravating because of its chronicity. It is described by the patients as a dull, transient pain behind the ear, persisting from one to 24 hours out of the week, either as a shooting pain centered around the ear, a dull annoying ache or throbbing in the neck over the carotid area, a drawing sensation or a pressure type of pain. The pain may be experienced in the jaw, and one patient expressed it by saying every tooth in the jaw ached. A common triad of symptoms is throbbing ache over the carotids, precordial pain and persistent frontal headaches.

Twenty-one of the 29 patients complained of chronic recurring headaches, most frequently occipital (10) or frontal (six), less frequently occipitocervical (two), generalized (two), fronto-occipital and temporal (one), and in the vertex (two). The syndrome of chronic headache in masked hypothyroidism was recently well emphasized by Fenichel.[1]

The majority were well developed and of normal weight, only one-third being overweight. They appear to be normal, alert people but tend to tire easily, and fatigue is a prominent symptom. Most frequently the pain appears when they are overly tired. One-half of the group were unduly sensitive to cold weather. Relatively few complained of dry skin or thinning hair. Insomnia was more characteristic than undue nervousness. Blood pressure readings were not remarkable.

There was usually a favorable response to thyroid, using small doses of .25 gr. three times daily, or a single dose of 1 gr. was generally favorable. Improvement was marked in 13, moderate in 11, and slight in four, with no improvement in one who was unable to tolerate even small doses of thyroid. The improvement was usually manifested after a latent period of approximately two weeks, which indicates the improvement was a response to thyroid extract rather than a psychogenic response, in which case the improvement would have been expected immediately after instituting therapy.

In summary, a few illustrative and abbreviated case histories are given.

Case Reports

Case 1. A 35 year old male was seen on March 10, 1949, complaining of pain in both sides of the neck (carotid area), frontal headaches and precordial pain of two weeks' duration. He had experienced very few headaches before, but for two or three years had complained of recurring pain or aching over the carotid areas, occurring once weekly and lasting a day or a day and a half. During the past two weeks he would awaken fresh but, as the day progressed, develop a nagging frontal headache. He was quite concerned about the aching in his neck and especially about the precordial pain. Physical examination revealed a well developed and well nourished male. His weight was 162 pounds, his height 67.5 inches. Ears, nose and throat were negative. Tonsils had been removed. Teeth were in good repair. Sinuses were clear. Thyroid was not enlarged; there was no cervical adenitis. The heart was of normal size and there was no murmur. Blood pressure was 110 mm. Hg systolic and 70 mm. diastolic; pulse, 80. Lungs were clear throughout. Abdomen and extremities were negative. The skin of the body was dry; the skin of the face was oily and there were a few comedos. The hair was fairly thick but receding. Roentgenogram of teeth and the electrocardiogram were normal. Red blood cells

TABLE I

Case	Patient		Age	Weight	Neuralgia	Headache	Fatigue	Sensitivity to Cold	B.M.R.	Resting Pulse	Improvement with Thyroid	Other Radiation of Pain
1	W. J. P.	(M)	59	N	Rt. temporal	None	+	−	−20	68	Moderate	Precordial
2	F. P.	(F)	45	N	Lt. frontal carotid bilateral	Occipital	+	+	−27	62	Marked	Precordial
3	R. S.	(F)	26	N	Post. rt. ear Rt. cervical	Fronta	+	+	−27	64	Moderate	Calf of legs
4	A. D.	(F)	48	N	Behind ears and post. cervical	Occipital	+	+	−18	68	Slight	—
5	G. L. V.	(F)	31	N	Rt. ear Rt. carotid	Generalized	+	+	−23	78	Moderate	—
6	R. T. D.	(M)	43	N	Lt. ear Lt. carotid	—	+	+	−10	62	Unable to take thyroid	
7	W. S. H.	(M)	58	N	Rt. temporal Rt. cervical	Frontal	+	−	−21	64	Marked	—
8	I. K.	(F)	29	O	Lt. ear	Occipital	+	−	−18	76	Moderate	Precordial
9	M. C. P.	(F)	59	O	Carotid bilateral	Frontal Occipital	+	+	−19	80	Marked	Upper chest
10	A. D.	(F)	36	O	Lt. ear Lt. cervical	Vertex	+	+	− 7	76	Slight	
11	L. S.	(F)	39	N	Carotid bilateral	—	−	+	−11		Moderate	Rt. arm
12	S. B.	(F)	23	N	Lt. carotid Lower jaw Lt. ear	—	−	−	−17	68	Moderate	Lt. shoulder

TABLE I—*Continued*

Case	Patient	Age	Weight	Neuralgia	Headache	Fatigue	Sensitivity to Cold	B.M.R.	Resting Pulse	Improvement with Thyroid	Other Radiation of Pain
13	L. A. W. (F)	23	N	Carotid bilateral	Occipital	+	+	−13	70	Marked	Gall bladder area
14	H. F. (F)	48	O	Behind lt. ear	—	+	+	−20	78	Marked	
15	V. B. (F)	28	O	Rt. facial Rt. ear	Rt. frontal	+	+	−23	70	Moderate	Sacroiliac Retrosternal
16	M. T. (F)	48	O	Lt. carotid	Occipital	+	−	−28	76	Slight	Rt. arm
17	F. L. (F)	44	O	Rt. post. cervical	—	+	−	−21	66	Slight	
18	F. E. W. (F)	43	N	Post. cervical	Generalized	+	−	−18	68	Marked	Precordial
19	J. C. (F)	42	N	Rt. facial	Frontal	+	−	−11	72	Marked	
20	M. R. (F)	33	O	Lt. frontal	Occipito-cervical	+	+	−16	68	Moderate	
21	I. Z. (F)	37	N	Lt. frontal parietal Ant. cervical	Occipito-cervical	+	−	−11	94	Moderate	Lt. sacroiliac, lt. groin
22	V. K. (F)	24	N	Lt. carotid	Frontal	−	−	−19	84	Marked	Epigastrium
23	M. B. (F)	23	N	Lt. frontal	Occipital	+	−	−15	66	Marked	Precordial
24	E. J. (F)	33	N	Lt. temporal	Occipital	+	−	−13	66	Moderate	Precordial
25	F. H. (F)	30	O	Rt. facial	Occipital	+	+	−14	62	Marked	Lt. upper chest
26	L. G. (F)	23	N	Lt. frontal retro-orbital post. cervical	Occipital	++	+	−12	62	Marked	LLQ
27	F. M. (F)	25	N	Rt. carotid Behind rt. ear	—	+	+	−17	72	Marked	
28	M. B. (F)	31	N	Rt. sternomastoid	Vertex	++	++	−12	76	Moderate	Generalized chest
29	W. F. (M)	35	N	Carotid areas	Frontal	−	−	−23	80	Marked	Precordial

5,800,000; hemoglobin, 108 per cent; color index, .93; white blood cells, 7,400; polymorphonuclear neutrophiles 58 (4), lymphocytes 40, monocytes 1, basophiles 1. Urinalysis was negative. On March 14, the basal metabolic rate was minus 23 per cent. Pulse was 80. Patient was started on thyroid one-quarter gr., three times a day. On March 21, patient still had a "nasty frontal headache" and some precordial pain, though the aching in his neck was relieved. Thyroid was increased to 1 gr. daily. On April 4 he was definitely improved and on May 26 was asymptomatic.

Case 2. A 23 year old female gave a history of recurring pain in the left frontal region, back of both eyes and in the back of the neck off and on for the past seven years. She had frequent headaches in the occipitocervical region or in both temples, lasting from one-half hour to an entire day, which had been more severe in 1945–1946, when they were a weekly occurrence, especially when she was fatigued. She also complained of frequent headaches at night or on arising in the morning. Patient was always nervous and tired, required a great deal of rest and was sensitive to cold weather. On December 12, 1947, she had vague pains in the left lower quadrant of the abdomen, though examination by a gynecologist was essentially negative except for cervicitis. Refraction was tested because of pain in left frontal area and behind the eyeballs, as well as recurring headaches. Ophthalmologic examination was likewise negative. On May 11, 1948, physical examination revealed a well developed and well nourished young female, not acutely ill. Her height was 62 inches, her weight 114 pounds. Ears, nose and throat were negative. Tonsils were absent. There was no sinus tenderness. Teeth were in good repair. Thyroid was normal. There was cervical adenitis. Chest was clear to percussion and auscultation. Heart was normal; blood pressure was 110 mm. Hg systolic and 72 mm. diastolic; pulse, 72. Abdomen was negative and without scars, and pelvis was normal except for slight cervicitis. Blood count and urinalysis were normal. Basal metabolic rate was minus 12 per cent. Pulse was 62, temperature, 98° F. In 1943–44 this patient had been given thyroid extract by two internists, starting with gr. one-quarter three times a day, which was gradually increased to gr. 11 daily, and started again in 1946 after a gynecologist had suggested that there were evidences of hypothyroidism. Accordingly, on May 11, 1948, she was again given thyroid extract, gr. one-quarter three times a day, and was relieved of headaches and facial pain in two weeks. On February 25, 1949, basal metabolic rate was minus 3 per cent, pulse 72, and temperature 98, and the same dosage of thyroid was continued. Unfortunately, a record of her old basal metabolic readings was not available. It is significant that the patient obtained marked relief from thyroid even though her metabolic reading was regarded as borderline.

Case 3. A 45 year old white female was seen on November 15, 1948, complaining of a smothering sensation in the chest anteriorly, pain in both sides of the neck (carotid area) and frontal headaches, and of being very nervous. Since June, 1948, she had been taking digitalis prescribed by a physician to relieve the discomfort in the precordium, though there was no apparent heart disease. On August 19, 1948, a metabolism test was done which showed a reading of plus 2 per cent, with pulse rate of 60 and temperature of 98° F. She received no medication and felt much better after a vacation. However, her symptoms soon recurred and persisted in spite of sedatives and estrogen therapy. By January 31, 1949, she was complaining of severe aching pain in the left anterior part of the chest radiating from beneath the sternum through to the back below the left shoulder blade. She also complained of left frontal headache and pain in the left upper jaw, as well as of a drawing sensation in the left side of her neck (carotid area). Physical examination was essentially normal. Her height was 64 inches, weight 120 pounds. Blood pressure was 110 mm. Hg systolic and 68 mm. diastolic; pulse, 64. Ears, nose and throat were negative. Tonsils were atrophic. Sinuses were clear to transillumination. Heart and lungs were normal. Abdomen and pelvis were negative. There was no history of change

of weight. Skin was of normal texture, though her hair was falling out excessively and she was quite sensitive to cold. On February 2 another metabolism test was taken, with a reading of minus 27 per cent. Pulse was 62, temperature 98° F. She was started on thyroid extract, gr. ss three times a day, and during the first week complained of left frontal headache and pain in the left upper jaw for two days. In two weeks she felt much improved and was relieved of all pain. Following this she was reëxamined at monthly intervals. She continued to improve in general and in her sense of well being, and remained asymptomatic.

Case 4. A 30 year old colored female was first seen by a physician on March 22, 1947, complaining of pain in the right facial region. This was diagnosed as possible facial neuralgia, which temporarily subsided under the influence of heat and aspirin but recurred at intervals. On September 16 she received infra-red therapy for vague pain in the left shoulder. On October 7 she was treated for vague abdominal pain, and on December 4 for a "sick headache." In December she received diathermy treatments to the upper lumbar region for backache. On several occasions she experienced a generalized headache, most severe in the temples and occiput. From January, 1948, on, she complained of nervousness, fatigue, pain around the right ear and frequent headaches. In February, 1948, she complained of feeling tired and sleepy all the time, and on February 27 experienced pain in the upper anterior portion of the chest. Physical examination was normal except for mild obesity; she weighed 144 pounds and measured 64 inches in height. Blood pressure was 100 mm. Hg systolic and 64 mm. diastolic. Urinalysis, blood count and roentgenogram of the chest were normal. On March 8, basal metabolic rate was minus 14 per cent; pulse, 62; temperature, 98.4° F. Patient was started on thyroid extract, gr. one-quarter, three times a day, and after 10 to 14 days was markedly improved. She continued on therapy for two months and then discontinued it. During the summer she again experienced pain in the right side of her face and had a questionable right lower premolar extracted. From September on, she had recurrent severe headaches and right facial pain, and on March 14, 1949, complained of neuritic pain in the right arm and leg. She was again started on thyroid extract, gr. one-quarter, three times a day, and in three weeks was relieved of her symptoms.

Case 5. A 31 year old female was seen on November 16, 1948, complaining of a neuralgic type of pain in the right ear which had recurred intermittently for the past six weeks. For the past year or two she had also experienced frequent headaches, which occurred especially at the time of her menses but also between cycles, and which persisted for from two to three hours up to several days. The headaches were generalized. The pain in the right ear also radiated down the right side of her neck to the carotid area. During the past year she had gained 10 pounds, was tired and sleepy most of the time, and was quite sensitive to cold weather. The menstrual cycle had been irregular since the birth of a child on July 2, 1947, and she frequently experienced amenorrhea for several months. Examination revealed a well developed young female; her height was 67 inches, her weight 140 pounds. Blood pressure was 120 mm. Hg systolic and 76 mm. diastolic. Ear, nose and throat examination was entirely negative except for cerumen in the right ear. Thyroid was normal. Chest was clear to percussion and auscultation. Heart was normal. There was a slight tenderness in the right lower quadrant, due to a small ovarian cyst. Patient was referred to the Ear, Nose and Throat Department on November 20, where a thorough examination, including transillumination and roentgenogram of sinuses, was essentially negative; the clinical impression was "mild facial neuralgia." On December 2 the basal metabolic rate was minus 23 per cent; temperature, 97° F., pulse, 78. Patient was then started on thyroid extract, gr. one-quarter, three times a day, with marked improvement in energy and relief of facial pain and headaches when seen in January and February, 1949. On May 12, 1949, she continued to feel well except for slight apprehension over impending operation for fibroid uterus.

Summary

Twenty-nine cases are presented illustrating a common clinical syndrome which is often overlooked, namely, atypical pain about the face and neck frequently associated with the hypothyroid state.

The pain is not severe, as in true facial neuralgia, but is rather a persistent and annoying ache. It is often associated with recurrent headaches and often with precordial pain.

The diagnosis is suggested by the above history and is substantiated by determination of the basal metabolic rate, as well as by exclusion of other disease by roentgen-ray study of the teeth sinuses.

Response to thyroid extract is generally favorable in two weeks.

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MYELOCYTIC LEUKEMIA: AN ANALYSIS OF INCIDENCE, DISTRIBUTION AND FATALITY, 1910–1948 *

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Leukemia was established as a distinct clinical entity in the middle of the Nineteenth Century. As Forkner [1] notes in his monograph a hundred years later, "We know almost nothing about its cause or its specific treatment."

Potassium arsenite, radiation and benzol were known by 1915 to produce marked clinical remissions in myelocytic leukemia. During the past four years, three additional agents—ethyl carbamate, the amine mustards, and perhaps the antifolic acid compounds—have been reported to effect distinct clinical improvement in the course of the disease.[2]

Adequate analyses of the final results of such therapy, in terms of longevity of patients with myelocytic leukemia, are extremely limited and all deal with radiation therapy.[3, 4, 5, 6, 7, 8, 9, 10, 11] The first and still the best of such presentations is the classic paper published in 1924 by Minot, Buckman and Isaacs.[3] No satisfactory detailed data are available in the literature regarding final results with the older chemical agents, and insufficient time has elapsed to evaluate the results with the newer agents.

The present report summarizes the pertinent statistical data available on the subject of incidence, distribution and fatality of individuals with myelocytic leukemia, in order to provide a foundation for comparisons between previous results achieved in the disease and information that will eventually be available with newer agents. The specific purposes of this communication are as follows: (1) to analyze statistics relative to age of onset, sex, duration of illness and fatality of patients with myelocytic leukemia, from clinical records available in three San Francisco hospitals; (2) to compare the data with similar reports available in the medical literature, and (3) to compare the data with mortality statistics compiled by the Bureau of the Census. Emphasis is placed upon the possible changes that may have occurred in these statistics during the past 40 years, and upon the possible rôle of therapy in such changes.

Data From San Francisco Hospitals

Clinical records were personally examined on patients with myelocytic leukemia seen at the University of California Hospital, Stanford University Hospital and the San Francisco City and County Hospital during the period

* Received for publication December 28, 1949.

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1910 to 1948.* The data were divided into three periods: patients seen 1910 through 1929, 1930 through 1939, and 1940 through 1948.

Inclusion of cases was made on the basis of an apparently definitely established clinical diagnosis of chronic myelocytic leukemia. In all but two cases (diagnosed only by necropsy), the clinical examination included study of the peripheral blood. After 1935, most of the patients had bone marrow aspirations. In approximately 30 per cent of the cases the diagnosis was confirmed by necropsy.

Cases of acute myelocytic leukemia were excluded in order to compare the present series with those in the medical literature. Approximately one-fourth of the cases in this series on whom necropsy was performed are recorded as having had acute leukemia, representing acute terminal exacerbation of chronic disease of established long duration.

Incidence: The number of patients with myelocytic leukemia seen before 1930, 1930 through 1939, and after 1940 is given in table 1. Only a relative degree of accuracy was possible in determining the incidence prior to 1930.

TABLE I

Myelocytic Leukemia: Data from Three San Francisco Hospitals, 1910–1948

	1910–29	1930–39	1940–48
Number of cases	54	62	96
Mean age onset, in years	39.6	42.3	43.6
Standard deviation of onset age	15.7	15.9	16.0
Per cent males	60.9	64.5	53.1
Mean age onset, males	39.1	42.2	44.9
Per cent females	39.1	35.5	46.9
Mean age onset, females	40.5	42.7	42.4

It is estimated that approximately 300,000 admissions to the three San Francisco hospitals from 1910 to 1930 were entered, but the lack of uniformity in records before 1920 undoubtedly involved errors and, in addition, possible loss of some cases of leukemia. From 1930 through 1939, there were approximately 270,000 admissions, and from 1940 through 1948, approximately 320,000 admissions.

Although a higher incidence of myelocytic leukemia relative to hospital admissions is suggested, no absolute significance can be attached to the observation. The possible errors in the records before 1920 already have been indicated. In addition, following 1935 there was accelerated interest in leukemia in this area, due to the pioneer trials of radiophosphorus,[11] with resultant increase in referrals of patients.

*We are greatly indebted to Dr. William J. Kerr, Dr. A. L. Bloomfield and Dr. Jesse L. Carr for permission to use the records, and to Dr. Lester Breslow, of the California Department of Public Health, for tracing many death certificates; to Miss Martha A. Buck and other record librarians for locating records and providing statistical information regarding admissions to the hospitals; and to Dr. E. Lucia for a careful evaluation of the manuscript.

Sex: Of the total 212 patients with myelocytic leukemia, 124 were males and 88 were females, or 58.5 per cent males. When the data are divided into three periods, as in table 1, there is a suggestion of a changing sex ratio. Whereas the ratio of males to females before 1940 is over 1.5, after 1940 the ratio drops to 1.1. The data are not entirely consistent and the differences, on the basis of the numbers involved, are not significant statistically.*

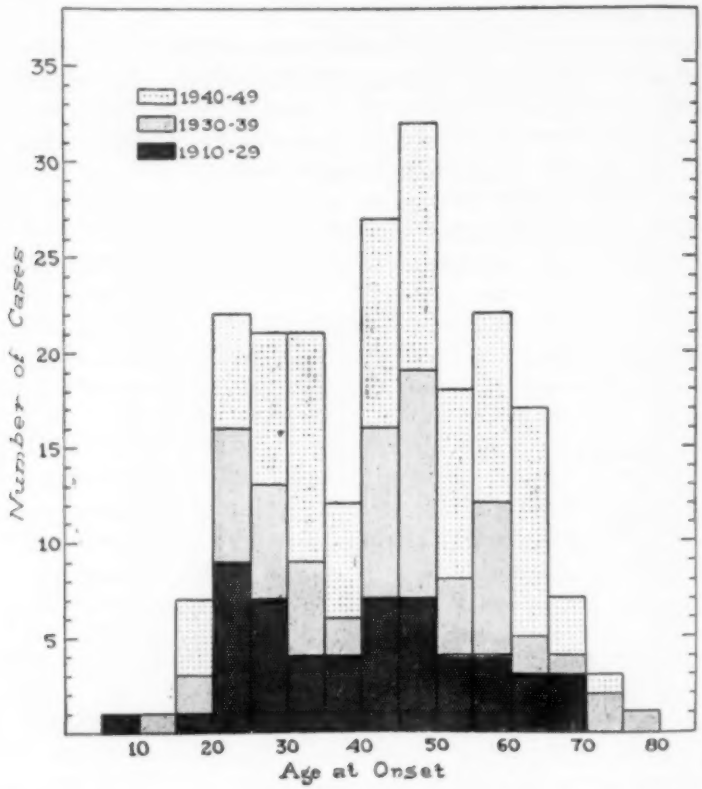

FIG. 1. Age at onset of myelocytic leukemia in 212 patients seen in three San Francisco hospitals, 1910–1948.

Data on the proportion of males to females in the general admissions to the University of California Hospital showed that there was a somewhat higher proportion of males in 1935 (44 per cent) than in 1925 or 1945 (41 per cent each). Correction of the ratios on this basis accentuates the predominance of males.

Age at Onset: The ages at onset of myelocytic leukemia are given in table 1 and in figure 1. The figures are based upon history of onset of

* Differences were considered "significant" if the probability was 0.05 or less that the difference could have occurred by chance. Differences are stated to be "highly significant" if the probability was 0.01 or less that the difference could have occurred by chance.

weakness, fatigability, pain or mass in the left upper abdomen, and bleeding or other similar symptoms suggestive of leukemia in patients subsequently demonstrated to have the disease. The mean period between the onset of symptoms and definite diagnosis was approximately 12 months. Rarely, the onset is dated from an accidental discovery of abnormal blood findings or palpable spleen in the course of examination for an apparently unrelated condition.

The average age of onset shows a consistent trend toward a higher age, averaging 39.6 years before 1930 and 43.6 years after 1940. This difference, however, is not statistically significant, due to the limited numbers and the wide spread of observations.

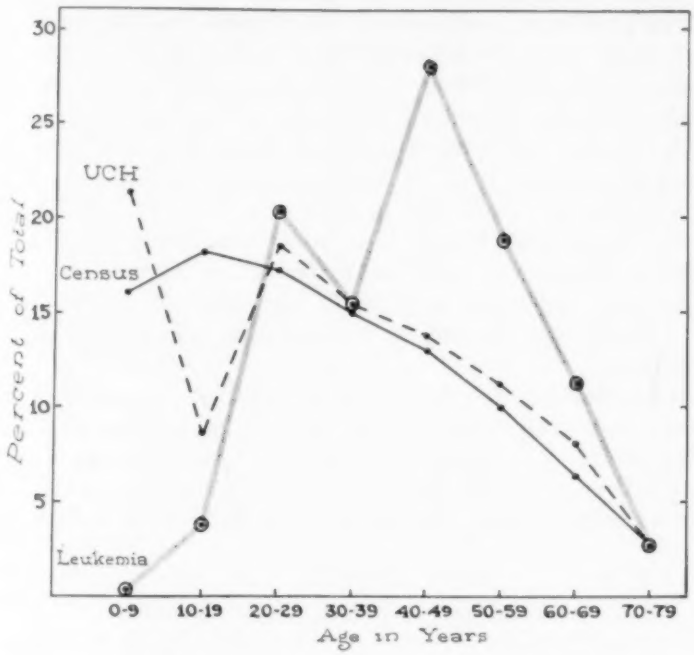

FIG. 2. Percentage distribution of 212 patients with myelocytic leukemia at age of onset (1910–1948) drawn against distribution of population, U. S. Census (1940) and hospital discharges (University of California Hospital, 1935–1945).

Analysis of the age at apparent onset among males and females (table 1) indicates no significant difference according to sex.

Figure 2 shows the distribution of the cases of myelocytic leukemia plotted with the percental distribution of the population of the United States (1940 census) and the admissions to the University of California Hospital (1935 and 1945), according to age groups. The peak of the incidence occurs in the fifth decade (40–49 years), indicated in either absolute numbers or in ratios against the two populations.

TABLE II

Duration of Myelocytic Leukemia: Data from Three San Francisco Hospitals, 1910–1948

	1910–29	1930–39	1940–48
Number of cases	45	55	73
Number of males	26	36	39
Number of females	19	19	34
Mean age onset, in years	40.7	41.9	45.6
Standard deviation of onset age	15.0	14.0	13.6
Mean survival, in years	3.1	3.0	3.2
Standard deviation of survival length	1.9	2.3	2.7

Duration of Illness: Table 2 records data on the length of life of patients with myelocytic leukemia, dated from apparent onset to death and divided into the three periods of observation. The groups comprise cases in which the date of onset could be estimated with some accuracy, and for which either hospital or death certificate information established the date of death. Also excluded from the series have been cases of myelocytic leukemia known to have been treated with radiophosphorus, since these are included in the recent report of Lawrence et al.,[11] reducing the total number from 212 to 173.

The mean survival of all 173 patients was 3.1 years (SD 2.3). One male and one female lived 11 and 17.5 years, respectively, after the onset of the disease; if these two cases are excluded for comparison with other medical literature, the mean survival is 3.0 years (SD 1.9). The mean duration of illness was the same in patients seen before 1930 and in those seen after 1940.

Analysis of the data relative to the survival of 173 patients according to sex shows a slightly longer mean survival in females (3.3 years) as compared to males (2.7 years). For 1910–29, the survivals in males and females are 3.0 and 3.3; for 1930–39, 2.8 and 3.0, and for 1940–48, 2.5 and 3.4 years, respectively. The differences, in view of the numbers and

TABLE III

Survival in Myelocytic Leukemia by Age Groups

Age	Minot[3]		Minot[2]		Hoffman[4]		Leavel[7]		Present data		Total	
	No.	Mean Years	No.	Mean Years	No.	Mean Years	No.	Mean Years	No.	Mean Years	No.	Mean Years
0- 9	—	—	2	2.00	—	—	—	—	1	7.0	3	3.7
10–19	2	2.50	4	3.41	2	4.19	2	1.0	6	2.7	16	2.8
20–29	9	3.72	15	3.43	18	3.50	9	1.5	30	3.5	81	3.3
30–39	21	2.66	20	3.66	25	3.61	21	3.3	24	2.9	111	3.2
40–49	13	3.73	14	4.00	12	3.38	23	3.3	55	3.1	117	3.3
50–59	5	2.01	17	3.64	9	3.02	20	3.0	33	2.8	84	3.0
60–69	2	2.70	6	2.34	5	2.88	6	3.3	21	2.9	40	2.9
70–79	—	—	—	—	—	—	2	0.7	3	2.7	5	1.9
Total	52		78		71		83		173		—	
Average		3.04		3.50		3.36		3.2		3.1		—

the wide ranges, are not statistically significant, but are considered worthy of note.

Confirming the analyses recorded by Minot et al.,[3] Hoffman and Craver [4] and Leavel,[7] the length of survival is not influenced by the age of onset of myelocytic leukemia. This is shown in table 3.

Of the total 173 cases, 121 are known to have received varying amounts and periods of radiation therapy. In general, local treatment to the spleen, with roentgen-rays or radium emanations, was usually the treatment of choice before 1925. During the fourth decade, "deep" roentgen therapy, often including the long bones as well as the spleen, appeared most often, while since 1940 total body irradiation was frequently used. In an additional 22 cases, radiation therapy was supplemented by potassium arsenite, benzol, and urethane or amine mustard. The mean survival periods in these groups of patients are given in table 4.

TABLE IV

Therapy and Survival in Myelocytic Leukemia: Data from Three San Francisco Hospitals, 1910–1948

	Cases	Survival, in Years	
	Number	*Range*	*Mean*
Radiation only	121	0.5–17.5	3.3
Radiation plus Fowler's solution	15	1.0–7.5	3.5
Radiation plus benzol	5	2.0–6.0	3.7
Radiation plus urethane, HN_2	2	3.0, 4.0	—
Fowler's solution only	8	0.9–6.0	2.5
Benzol only	2	0.6, 5.0	—
None	20	0.5–6.0	1.7

Table 4 also presents the figures on 30 patients who are not known to have received radiation treatment. Of these, eight were treated with potassium arsenite only, and two with benzol only. In 20 patients only supportive therapy, such as transfusions, appears in the clinical records. The selective nature of this group, which lived an average of 1.7 years after apparent onset of the disease, is obvious from the examination of the clinical records. The group includes patients so severely ill on entry that the scheduled radiation therapy was not delivered, cases in which the leukemia was complicated by severe intercurrent infections such as tuberculosis, two cases who underwent splenectomy, and an accidental traumatic death from rupture of the spleen.

Statistical comparison between the 30 cases which presumably received no radiation and the 143 cases which were treated with radiation reveals a highly significant difference. It is obvious, however, that this difference is not necessarily attributable to the type of therapy, but also represents a natural selection or grouping of patients with short prognosis in the untreated series, as pointed out in the preceding paragraph.

Figure 3 presents the cumulative survival of the total group of 173 patients. It is to be seen that 47 per cent of all patients lived three years or longer after the apparent onset of the disease; 16 per cent survived five years or longer, and two patients lived over 10 years. The data of table 2 show clearly that, by the criteria used, there was remarkable consistency in the average period of survival of patients with myelocytic leukemia during the past four decades. The prognosis of the average case, so far as length of life from apparent onset is concerned, was no better after 1940 than it was in, say, 1920.

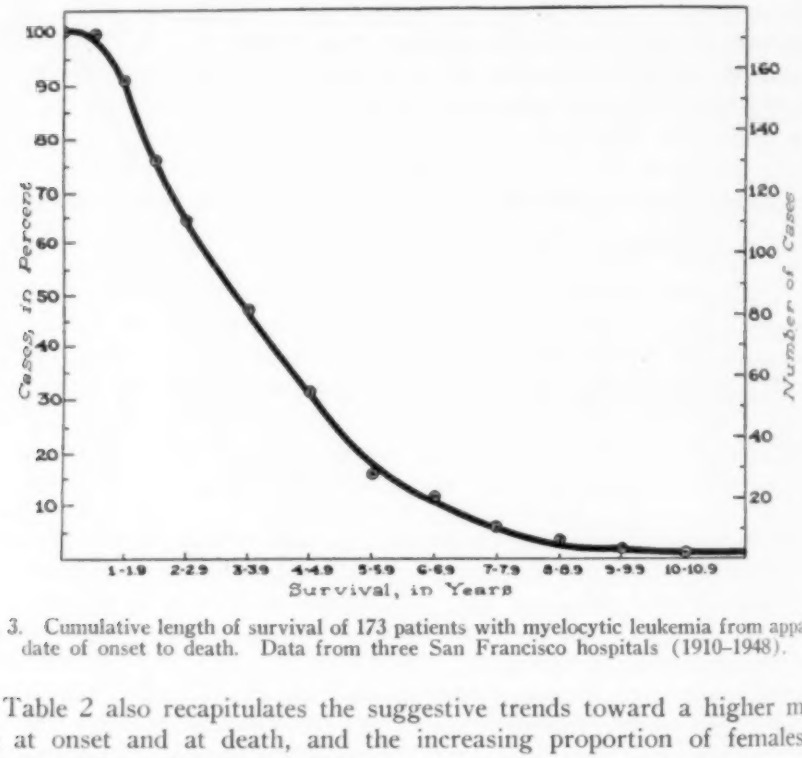

FIG. 3. Cumulative length of survival of 173 patients with myelocytic leukemia from apparent date of onset to death. Data from three San Francisco hospitals (1910–1948).

Table 2 also recapitulates the suggestive trends toward a higher mean age at onset and at death, and the increasing proportion of females in patients with myelocytic leukemia.

DATA FROM MEDICAL LITERATURE

The extensive literature on myelocytic leukemia contains few reports with data that can be used statistically. Nine papers,[3, 4, 5, 7, 8, 9, 10, 11, 12] as summarized in table 5, present detailed information regarding the age and sex of patients. Seven reports,[3, 4, 5, 6, 7, 10, 11] as given in table 6, also include specific data regarding the duration of the disease.

Sex: Of the total of 975 cases of myelocytic leukemia tabulated in table

TABLE V

Myelocytic Leukemia: Onset of Disease by Age

Author and Reference	Center	Date	Cases Total	Male	Female	0–9	10–19	20–29	30–39	40–49	50–59	60–69	70–79	80–89	Average	SD
Ward[12]	England	to 1917	247	136	111	7	12	25	84	60	30	22	5	2	40.9	15.0
Minot[3]	Boston	1898–1923	166	93	73	3	6	30	51	37	23	15	1	—	40.0	14.0
Hoffman[4]	New York	1917–1930	80	55	25	—	2	18	26	15	13	6	—	—	40.2	13.5
McAlpin[5]	New York	1919–1929	24	13	11	—	1	2	8	7	5	1	—	—	41.7	16.8
Leavel[7]	New York	1917–1936	87	46	41	—	2	9	25	23	20	6	2	—	43.7	14.1
Wintrobe[8]	Baltimore	1926–1945	58	34	24	1	2	8	18	8	13	8	—	—	41.6	15.4
Bethell[9]	Michigan	1927–1941	131	68	63	1	6	12	27	32	32	18	2	1	46.0	14.6
Krebs[10]	Denmark	1931–1946	55	27	28	1	3	5	11	13	15	5	2	—	44.4	15.4
Lawrence[11]	California	1936–1947	127	72	55	—	11	21	27	30	26	10	2	—	41.1	15.9

5, 544 (or 55.8 per cent) were males. It is of interest, however, that the percentage of males in 517 cases seen up to 1930 [3, 4, 5, 12] was 57.4, whereas in 313 cases seen up to 1947 [9, 10, 11] the percentage of males was 53.3. This finding is in agreement with the trend seen in the presently reported data, and suggests an increasing proportion of females with myelocytic leukemia. A recent additional article from Scandinavia [13] indicates a slight preponderance of females over males in a small series: 33 males as compared with 46 females.

Age at Onset: The reports on myelocytic leukemia do not break down the cases according to dates, but 517 cases seen up to 1930 show an average age at onset of 40.5 years (SD 13.8). The last three reports, on 313 patients seen from 1927 to 1947, indicate an average age at onset of 43.7 years (SD 14.2). The difference is highly significant statistically. This finding is in conformity with the trend observed in the presently reported data. Krebs and Bichel [10] also note that their material on their 55 cases contained a higher percentage of elderly patients than previously published statistics. The mean age of all patients admitted or seen in the centers is not

TABLE VI

Myelocytic Leukemia: Duration of Disease

Author and Reference	Center	Date	Cases Total	Survival, up to number of years:										Mean*	SD
				1	2	3	4	5	6	7	8	9	10+		
			No.											*Years*	
Minot et al.[3]	Boston	1898–1923	52	7	13	9	10	8	2	2	1	—	—	3.0	1.3
Minot et al.[3]	Boston	1898–1923	78	4	15	18	18	10	5	2	3	2	1	3.5	1.5
Hoffman[4]	New York	1917–1930	75	5	23	11	9	10	6	5	2	—	4	3.4	1.3
McAlpin[5]	New York	1919–1930	18	1	1	8	4	2	1	1	—	—	—	3.0	2.1
Arendt[6]	Zurich	to 1931	39	2	4	6	10	3	6	3	3	—	2	3.9	1.0
Leavel[7]	New York	1917–1936	87	19	13	18	16	4	7	2	2	2	4	3.2	1.1
Krebs[10]	Denmark	1931–1946	44	—	11	7	8	6	4	3	2	3	—	3.4	2.8
Lawrence[11]	California	1936–1947	110	4	24	26	27	7	12	8	—	1	1	3.7	1.6
Present data	California	1910–1948	173	16	46	29	27	26	8	10	4	5	2	3.0	1.9

* Excluding cases living 10 years or more.

given, and the evidence from census statistics would suggest that this greater mean age in the leukemia patients is a reflection of the advancing mean age of the population as a whole, and such population as is seen in the hospitals.

Duration of Illness: Table 6 presents eight series of patients with myelocytic leukemia in which adequate data are available regarding their survival from the apparent onset of the disease. Only one group, reported by Minot et al.[3] in 1924, was "untreated" in that the patients received no radiation therapy. All other reports studied the survival of patients who had received radiation therapy, delivered from external sources or as radiophosphorus.[11]

Two reports are available regarding the influence of sex upon the duration of illness. Hoffman and Craver [4] found an average of 3.4 years for males and 3.27 for females, whereas Krebs and Bichel [10] record 40.7 months for males and 41.5 months for females. These figures do not support the trend suggested in the presently reported data to the effect that the survival is slightly longer in females. In neither of the series are the differences of statistical significance.

Table 3 summarizes the effect of age at onset on the prognosis in myelocytic leukemia. There is no significant or consistent correlation, indicating that the mean life span is the same in patients who develop myelocytic leukemia at a younger or at an older age.

As given in table 6, the mean survival in all groups was between 3.0 and 3.9 years in length; the means do not include the 12 patients who lived for more than 10 years. Statistical evaluation shows highly significant prolongation of survival when the figures on the "untreated" cases of Minot et al.[3] are compared with those of Arendt [6] or of Lawrence.[11] In fact, there is a statistically significant difference between Minot's untreated cases and those treated with radiation.

Such comparisons are not entirely valid, particularly when they are made between figures gathered before 1924 [3] and cases seen in other centers 10 to 20 years later. Even in Minot's groups, no indication is present regarding the possible rôle of selection of patients grouped in the two series. There is not a single study available in the literature in which alternate cases, without selection, were treated by one form of therapy or another.

It is of interest to compare the figures of Lawrence et al.[11] on 110 patients treated with radiophosphorus who died by the time of the report, with the 173 patients gathered in the present study. On over-all comparison, the difference in survival, 3.7 years and 3.1 years, respectively, is statistically highly significant. If only those cases which received radiation therapy are considered, the mean survival of 3.3 years remains sufficiently different from the figures of Lawrence et al. to be statistically significant. Nevertheless, there can be no definite conclusion that radiophosphorus prolongs the life of patients with myelocytic leukemia. Many of the patients reported by Lawrence et al. were treated on an ambulatory basis, which indicates selec-

tion of cases who were in better clinical condition at the onset of therapy. The present report includes many patients who were terminally ill at admission, and the obviously selective nature of the untreated group of 20 has already been stressed. The difference in the figures, therefore, can well be attributed to the natural selection that occurred in both groups, and not necessarily to the therapy involved. It should also be noted that the majority of patients reported by Lawrence et al. received roentgen therapy in addition to radiophosphorus. The mean survival period of 26 patients treated exclusively with radiophosphorus and who had died was 2.3 years; this figure is obviously low, because eight patients were still alive, and the mean survival of all 34 at the time of the report was 3.2 years.

Another approach to such comparisons is made by evaluating three groups [3, 4, 5] for a total of 171 cases treated up to 1930 with two groups for a total of 154 cases treated from 1931 to 1947.[10, 11] The mean survival periods are 3.4 and 3.6 years, respectively, a difference well within chance occurrence. Over-all, with treatment available during these two periods in the centers reporting, the prognosis in myelocytic leukemia relative to longevity has not been altered appreciably.

Analysis of the total data of table 6 indicates that approximately 50 per cent of all 676 patients lived up to three years, and that approximately 20 per cent lived five years or longer after the clinical onset of the disease. Approximately 2 per cent (14 patients) lived 10 to 17.5 years, and survivals up to 20 years have been recorded.[14, 15]

Data From Vital Statistics

In the extensive statistical analysis of cancer mortality in the United States, published by Gover in 1939–41,[16] no consideration is devoted to leukemia. Examination of data on this subject available in the annual mortality statistics compiled by the Bureau of the Census was therefore undertaken. A similar report was recently prepared by Sacks and Seeman.[18] The shortcomings of such data have been emphasized repeatedly.[16, 18] In relation to leukemia, additional factors which must be considered are that

Table VII

Population, Deaths and Deaths from Leukemia, U. S. Death Registration States, 1910–1940

	Total:				Leukemia:			
	Population	Males	Deaths	Male Deaths	Deaths	Male Deaths	Deaths per Million Population	Deaths per Thousand Total Deaths
	millions	*per cent*	*thousands*	*per cent*	*number*	*per cent*		
1910	47	51.5	805	54.6	864	62.8	18.2	1.1
1920	86	51.0	1,118	52.4	1,676	59.4	19.4	1.5
1930	117	50.6	1,327	54.3	2,508	59.2	21.4	1.9
1940	132	50.2	1,417	55.8	4,646	58.5	35.2	3.2

"leukemia" is first recorded apart from "anemia" in 1910, and that "Hodgkin's disease" is first separated from "true leukemia" in the mortality statistics for 1921. No distinction is made between myelocytic, lymphocytic and monocytic leukemia, nor between acute and chronic cases of these diseases.

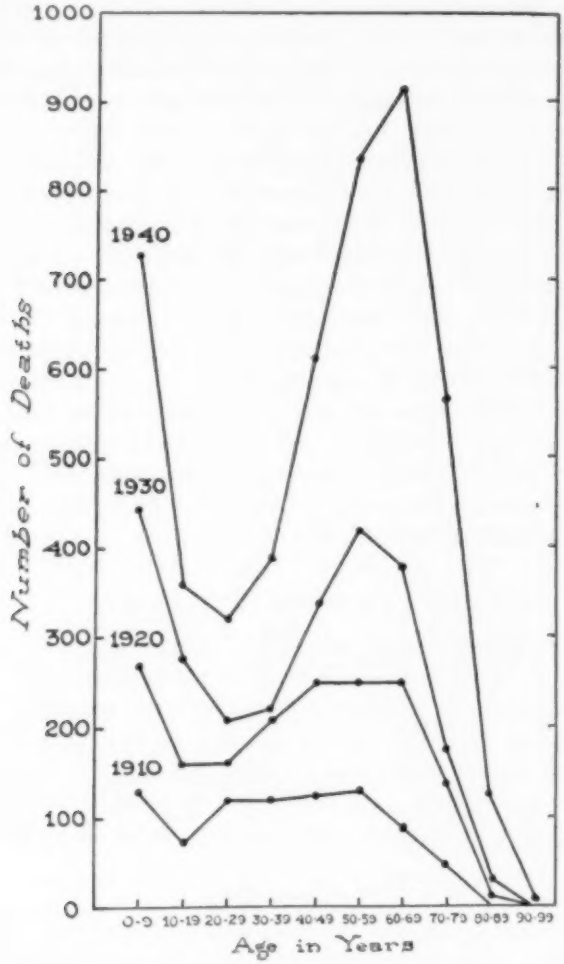

FIG. 4. Absolute number of deaths from leukemia according to age, in the United States Death Registration States, 1910–1940 (data from U. S. Bureau of the Census, Mortality Statistics, years indicated).

Incidence: Table 7 shows the absolute numbers of *recorded* leukemia deaths during the years of the last four national censuses. These data are given according to age groups in figure 4. There is a steady rise (from 18.2 per million in 1910 to 35.2 in 1940) in the ratio of deaths from leukemia to the total population. It is impossible to determine whether

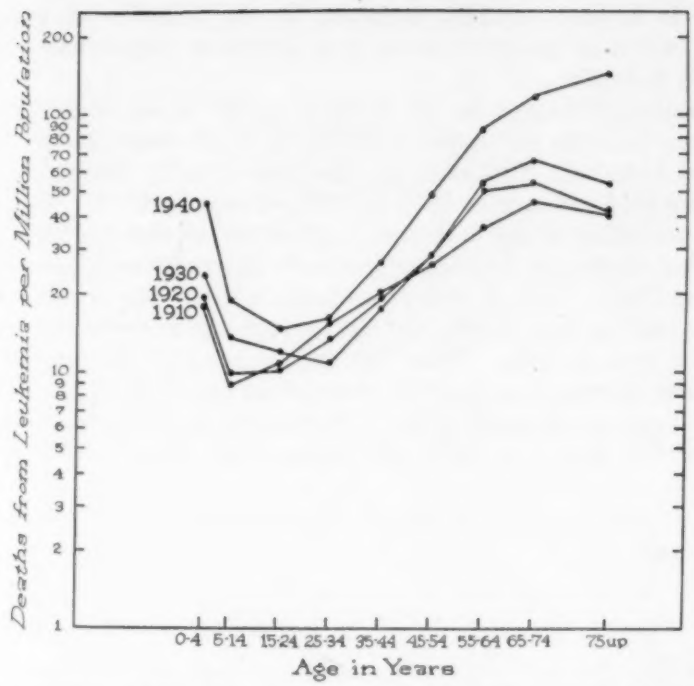

FIG. 5. Number of deaths from leukemia per million living population, United States Death Registration States, 1910–1940 (data from U. S. Bureau of the Census, Mortality Statistics, years indicated).

this represents a true increase, or is attributable to improved diagnoses and improved reporting of the diseases. Figure 5 presents the data plotted according to age. There is a relatively high incidence during the first decade, and a progressive increase in the number of deaths from leukemia per living population from the third to the seventh decade.

The higher mean age at death with leukemia in the census mortality figures as compared with statistics derived from hospital records and medical

TABLE VIII

Deaths from All Causes and Deaths from Leukemia, Less All Deaths under 10 Years of Age, U. S. Death Registration States, 1910–1944

	Total Deaths 10–100 Years of Age in Thousands	Average Age at Death	Leukemia Deaths 10–100 Years of Age	Average Age at Death	Leukemia Deaths
	number	*years*	*number*	*years*	*per cent*
1910	537	52.2	729	43.5	0.14
1920	846	54.8	1,402	45.7	0.16
1930	1,109	58.0	2,071	47.0	0.18
1935	1,214	60.0	3,012	48.7	0.25
1940	1,267	62.3	4,160	50.2	0.32
1944	1,264	63.3	4,805	52.2	0.39

literature is at least partially explained by the inclusion of lymphocytic leukemia, which is known to occur at a somewhat higher mean age than myelocytic leukemia.

The ratios of the number of deaths from all causes to the number of deaths from leukemia are shown in table 8, in which deaths below the age of 10 are not included. This ratio also has risen steadily during the past 30 years, from 0.14 per cent in 1910 to 0.39 per cent in 1944. The data are recorded according to age in figure 6, which shows that the ratio is at its peak during the second decade and gradually decreases with advancing age.

Age at Death: Table 8 also presents the average age at death from all causes beyond the first decade, and the average age at death from leukemia during the same periods. There has been a constant and almost parallel rise in these figures; thus, in 1910, the average age of death from all causes was 52.2 years as compared with 43.5 years in the leukemia group, a difference of 8.7 years; by 1944, the figures had risen to 63.3 and 52.2,

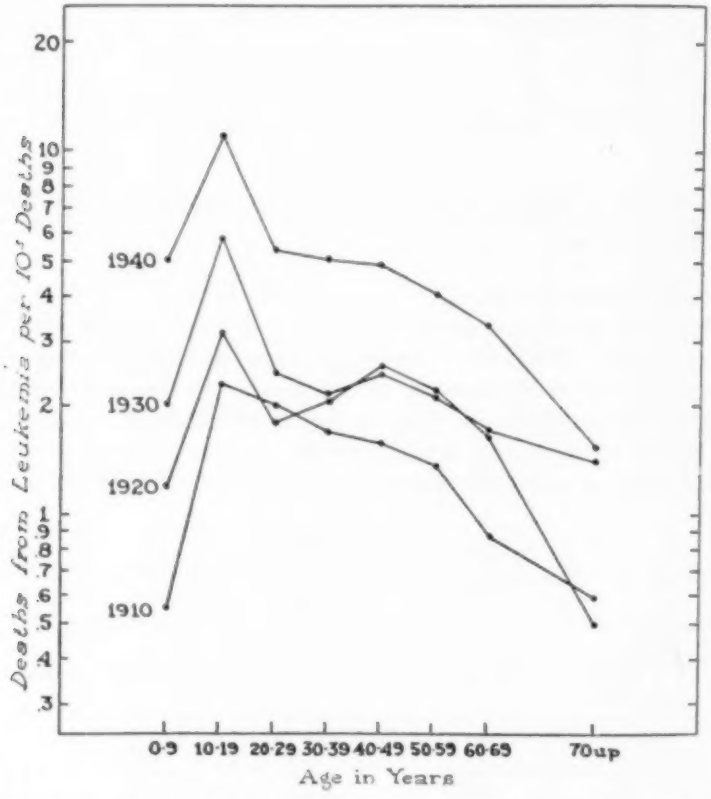

FIG. 6. Number of deaths from leukemia per 1,000 deaths, United States Death Registration States, 1910–1940 (data from U. S. Bureau of the Census, Mortality Statistics, years indicated).

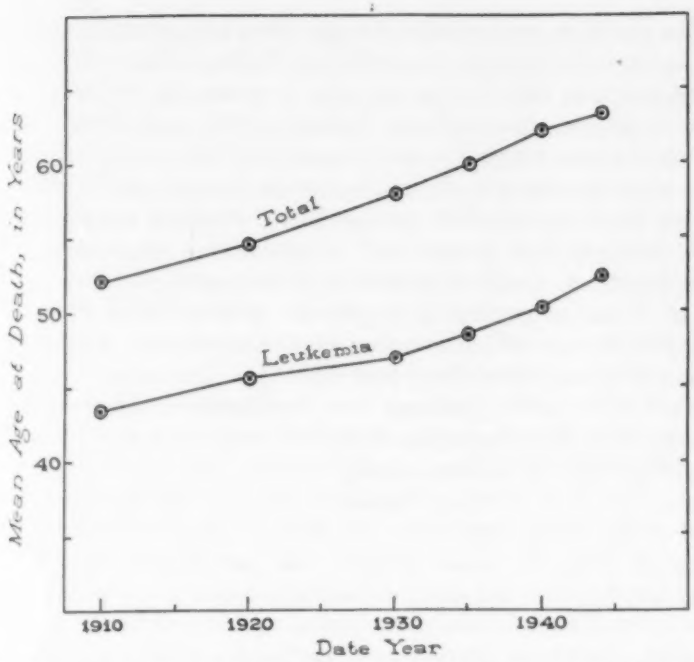

FIG. 7. Mean age at death of total deaths and at deaths from leukemia, less cases of both categories dying before 10 years of age, U. S. Death Registration States, 1910–1940 (data from U. S. Bureau of the Census, Mortality Statistics, years indicated).

respectively, or a difference of 10.1 years. The data, graphically shown in figure 7, indicate that the population which dies of leukemia has an average survival period that is a decade shorter than the general population, but that the factors which have increased the life-span of the general population by 11 years during the past 30 years are also reflected in the population which dies of leukemia.

Sex: An additional interesting finding recorded in table 7 is that the proportion of males to females dying of leukemia has decreased steadily from 62.8 per cent in 1910 to 58.5 per cent in 1940. The significance of this recorded trend is not apparent at present. The same trend is maintained when the leukemia ratios are adjusted for the proportion of male to female deaths from all causes, so that this trend is not accountable on the basis of a shift in the sex ratio of the total death figures.

DISCUSSION

On the basis of the foregoing analysis of data from three sources, several conclusions may be drawn.

In regard to *incidence,* statistics from San Francisco and United States vital statistics both show consistent trends toward a continually higher number of cases of chronic myelocytic leukemia. These trends are main-

tained when the data are corrected for age distribution, and are evident also as ratios against population or number of deaths. Nevertheless, it is impossible to conclude that a true increase in leukemia, or more specifically myelocytic leukemia, has occurred between 1910 and 1948, because the relative rôle of better diagnosis, better reporting, better filing of records and, locally, increase in referrals of patients cannot be evaluated. Whatever the factors may be, it is true that an increasing absolute number of cases of myelocytic leukemia will be seen and recognized by physicians, so that the clinical management of such cases will be an increasing problem. It has been pointed out [18] that at present more persons in the United States die from leukemia than from smallpox, meningococcus meningitis, scarlet fever, poliomyelitis, malaria, typhoid fever and diphtheria *combined*.

In regard to *sex ratios*, evidence from local sources, the medical literature and vital statistics all indicate that there has occurred a definite shift toward a higher proportion of females among patients with myelocytic and other leukemias. This shift is not attributable entirely to the increasing proportion of females in the living population, nor to any increase in the proportion of females dying from all causes. During the past 40 years there have been increasing employment and participation of women in industries and, therefore, exposure to such agents as radiation and benzol, both of which have been at least tentatively incriminated in occasional cases of the disease.[19] Whether these factors play a rôle is purely hypothetic, but they suggest an area for further investigation.

In regard to *age of onset*, or age at death, statistics from all three sources definitely show that there has been a progressive increase. This is probably due to a progressively older population in the United States (and Scandinavia) since 1910, and a progressively older age at death from all causes. It is not possible to interpret the findings, on the basis of available data, as being due to a true later age of onset, perhaps as a result of some increasing "resistance" of the population to the disease. What can be stated, however, is that there will be increasing numbers of patients in older age groups with chronic myelocytic and other leukemias seen by physicians. By the present criteria of onset, based essentially on history, the increasing mean age of death cannot be attributed to longer survival or better prognosis.

In regard to *duration of illness*, all figures from local sources or in the medical literature show conclusively that, by the criteria of measurement available, there has been no significant change in the prognosis of patients with chronic myelocytic leukemia during the past 30 years. The mean survival persists stubbornly at three to four years after apparent onset; approximately 20 per cent of the patients live for five years or longer, and approximately 2 per cent survive for 10 years or longer. Local data suggest that the survival is slightly, but not significantly, longer in females, but this is not substantiated by the medical literature. The age at onset of the disease plays little or no rôle in the prognosis as far as longevity is concerned.

It is quite obvious that there is no method or procedure known at present which will alter the eventual prognosis of myelocytic leukemia. Data on radiation therapy and radiophosphorus suggest that some prolongation of life is achieved, but no adequate control groups for comparison are available. Reference is often made to the group of 52 untreated cases collected by Minot et al.[3] before 1924. Such comparisons are not valid for several reasons: (1) The degree of selection in this group, differentiating it from the group treated by radiation, is unknown. (2) Patients seen before 1924 are not representative of patients seen 20 years later in other areas. (3) Many of these untreated cases received measures other than radiation, such as potassium arsenite. In the data gathered locally, the selective nature of 20 untreated cases is obvious, and they cannot validly be compared with patients who received radiation therapy.

Final clinical data on the effect of chemical agents used in leukemia, such as benzol, potassium arsenite and, more recently, the amine mustards and urethane, are too few, too recent or too generally presented to evaluate their possible usefulness insofar as prolongation of life is concerned.

It should be emphasized that even a clear-cut demonstration that a certain type of therapy is not curative, or does not prolong life appreciably, is not to be considered as an indication against the use of such therapy. Ample clinical evidence is available that roentgen therapy increases the *effective* life span of patients with leukemia, converting exacerbations of the disease into clinical remissions. Although such remissions are apparently not reflected by demonstrable increases in the absolute life span, the relief to the patients is sufficient indication for such therapy until better methods may become available.

It should be noted, however, that if the purely palliative nature of roentgen or other available therapy is recognized, the desirable mode and dosage of such therapy should be the minimum to produce the desired results. An interesting discussion on this point is given by Krebs and Bichel[10]: "If we survey the by now considerable literature on irradiation therapy in leukosis, we find that most of the authors think that this therapy in a number of cases can be directly lifesaving. The irradiation must therefore have been the means of prolonging the life of such patients. But apart from this it is also difficult to understand, on general principles, that it should not be possible to prolong the life of the patients, considering that the irradiation improves their general condition and this makes them better able to resist intercurrent affections. That this does not find expression in a longer duration of life statistically, may be due to a variety of causes. In the first place it must again be remembered that the non-irradiated patients used as material for comparison were treated in a different way, and therefore perhaps lived longer than the non-treated. Further, it is possible that the excursions are too few and too slight to affect the statistical results. And finally it is possible that the irradiation treatment in certain cases

shortens the life of the patient, while in others it prolongs it. That this is so, is not improbable. The authors on leukosis therapy time and again warn against overdosaging. . . . It is difficult to determine in the individual case whether the lethal issue has been hastened by a too intensive irradiation therapy, but there are examples enough which might indicate that such has been the case."

None of the agents or procedures used in the clinical management of myelocytic leukemia is curative, and final evaluation of their relative value must be made on the statistical determination of the possible prolongation of life that may be achieved. If no prolongation of life can be demonstrated, the choice of therapeutic management must be based on such factors as degree of amelioration, comfort of the treatment to the patient, and ease and availability of the procedures.

In gauging the duration of illness in myelocytic leukemia, it should be recognized that it is based on the time of onset as determined by the patient's history. This, in many cases, is notoriously unreliable. Unfortunately, timing the duration from the date of diagnosis [3, 4] or date of initiation of therapy [16] is no more informative, and such statistics are entirely in parallel with determinations based on history and substantiated by clinical examination. The truth of the matter is that the real demonstration of effect of therapy is the *cure rate*, such as is possible to achieve in, say, cancer of the breast. Present knowledge of myelocytic leukemia and its onset is so incomplete that its acceptable diagnosis, in the stage of peripheral blood involvement or, at the best, widespread bone marrow involvement, is comparable to, say, diagnosing carcinoma of the breast by the presence of pulmonary or osseous metastases.

Many interesting and important facts regarding leukemia, particularly those which require statistical analysis, are at present impossible or extremely difficult to demonstrate because of the limited number of cases seen by even the largest centers. According to vital statistics, more than 5,000 people die of leukemia each year in the United States. Of these, approximately 2,000 would be classified as chronic myelocytic leukemia. Considering that there are some 1,500 roentgen therapists and over 330 centers recognized for resident training in roentgenology, no one center can anticipate procuring, within a reasonable period of time, sufficient statistically usable data for the evaluation of new types of therapy being introduced for leukemia. The largest detailed series of patients with myelocytic leukemia, even regarding such basic data as sex or age of onset, are those of Ward,[12] on 247 cases, reported in 1917, and the present group. The largest series for the final evaluation of therapy are those of Lawrence et al.[11] and the present group. The wide spread in the observations in this disease make such numbers inadequate, especially when the groups have to be further subdivided. For example, the conclusions regarding the shifting sex ratio and the increasing age at onset are brought out in the present report on combined data, simply

because such facts are obscured in any individual report on a limited number of observations. It is also useful to reflect that, although benzol and potassium arsenite have been available for over 50 years, not a single adequate series using these agents is presented in the literature.

The sound evaluation of therapeutic agents, as well as other information, necessitates a systematic plan of study in addition to a numerically adequate supply of cases. Such a plan involves either the control of the natural or biased selection of patients, or the establishment of criteria by which such selection can be interpreted. The limited number of patients for such studies requires a plan that would be accepted and followed by many institutions, with central collation of the information.

Examination of the available information indicates clearly that the experience of 40 years has been inadequate to indicate the best methods for the management of myelocytic and other leukemias. Recommendations of astute, experienced clinicians are based on impressions and individual cases, and not on statistically demonstrable facts. This situation will continue unless a nation-wide plan on a systematic therapeutic trial, so effectively carried out in the fields of antibiotics and in hormonal treatment of advanced mammary cancer, can be developed for myelocytic leukemia.

Summary

Statistics are presented regarding the age of onset, sex, duration of illness and mortality of 212 patients with chronic myelocytic leukemia seen in three San Francisco hospitals, 1910–1948. The data are compared with nine similar reports in the literature, comprising a total of 975 patients. The data are further compared with United States mortality statistics for leukemia during the period 1910–1944.

All data show a continually higher incidence of leukemia, although it is not possible to establish whether this represents a true increase or is due to improved recognition and reporting.

From 1910 to 1948 there has been a progressive and consistent shift in the sex ratio toward a higher proportion of females in patients with myelocytic and other leukemias.

From 1910 to 1948 there has been a progressive and consistent shift toward a higher age at onset or at death of patients with myelocytic and other leukemias. This is probably due to a progressively older living and dying population of the United States.

The duration of illness from chronic myelocytic leukemia, as determined from age of apparent onset to death, shows no significant change during the past 30 years. The mean survival is three to four years, with 20 per cent living five years or longer and 2 per cent living 10 years or longer.

No form of therapy can be stated to increase the life span of patients with myelocytic leukemia, although such therapy is definitely ameliorative

and palliative. Available statistics regarding evaluation of therapy involve selection which negates direct comparison of different methods.

The implications of the study and recommendations for a nation-wide therapeutic trial of various agents in leukemia are discussed.

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CASE REPORTS

MARKED EOSINOPHILIA WITH CANCER: A POOR PROGNOSTIC SIGN *

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There are many causes of eosinophilia. Wintrobe [1] has listed and discussed the diverse conditions in which eosinophilia appears. However, only the following lines referable to cancer appear in this textbook about a miscellaneous group of disorders in which eosinophilia occurs: "Tumours of the ovary, various other neoplasms, especially those involving serous surfaces or bones or when necrosis of tumour tissue occurs." Scant attention to this finding in cancer was given in the American literature until the appearance of the report by Isaacson and Rapoport [2] in 1946. They collected from the literature 19 cases of pronounced eosinophilia with cancer (over 10 per cent in the differential count), only three of which had appeared in the American literature. In addition, Isaacson and Rapoport added 15 new cases of malignant tumor in which marked eosinophilia was a feature.

In 27 of the 34 cases presented (or 90 per cent), metastases were definitely shown. In two of the other seven, metastases were suspected but not proved. In only one case were metastases not proved or suggested. The other four case reports did not give sufficient information to determine the presence of metastases. Of the 27 cases with proved metastases, the liver was involved in 17.

Twenty-nine of the 34 cases were of epithelial origin and five were of connective tissue origin. Cases of carcinoma of the uterus, cervix, breast, penis, thyroid, adrenal, pancreas, lung, stomach, gall-bladder and colon, as well as four cases of sarcoma, were included in the group. Of the 34 cases, carcinoma of the colon was present in seven, the largest number in a single organ. Isaacson and Rapoport concluded from their study that the occurrence of eosinophilia with malignant tumors was usually indicative of dissemination and significant of a poor prognosis.

We have found three reports, not previously mentioned, in which eosinophilia occurred with malignant growths. Bernard, Marie and Anchel [3] presented a case of carcinoma of the lung with pleural effusion in which 56 per cent of the cells of the pleural fluid were eosinophils and there was a blood eosinophilia of 11 per cent. Stickney and Heck,[4] in a general discussion of eosinophilia (over 6 per cent in the differential white cell count), reported a total of 418 cases. In tabulating the cases by the degree of eosinophilia, malignant lesions were found in 5 per cent of the 6 to 10 per cent eosinophil count group, 1.3 per cent of the 10 to 20 per cent group, and 4 per cent of the above 20 per cent group. One is not

* Received for publication March 10, 1950.
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able to determine from the data given the exact number or type of malignant tumors. The authors stated that if there is any special causative factor in eosinophilia in the presence of malignant lesions, it may be metastatic involvement of the liver, since this occurred several times in their experience. They also noted that any process that destroys the substance of the liver, such as cirrhosis or carcinoma, may be associated with eosinophilia.

Harvier, Pestel and Marche [5] presented a patient with hepatomegaly and leukocytosis. The white blood cell counts varied from 15,000 to 31,000 per cu. mm. The eosinophils in the differential count varied from 31 per cent to 51 per cent. A biopsy of an enlarged cervical lymph node revealed histologic findings consistent with carcinoma, the origin of which could not be ascertained. Recurrent ascites developed with rapid progression of the disease at the final examination reported. To these cases of malignant tumor with eosinophilia, we are adding another.

Case Report

A 52 year old white unemployed male was seen for the first time on May 4, 1949, in the outpatient department. He had been in his usual state of good health until six weeks previously, when he experienced moderately severe epigastric pain aggravated by meals and relieved by belching and expulsion of flatus. There was no anorexia, nausea, vomiting, diarrhea, constipation, melena or jaundice. There had been a weight loss of 10 pounds in the previous month. There was no previous illness, injury, hospitalization or operation. His parents had died of cancer, sites unknown. System review was negative. There was no history of hay fever, asthma, urticaria, migraine, or any other allergic manifestations. He was a moderate drinker, with an average consumption of 10 glasses of beer daily and six "shots" of rye weekly. On physical examination the patient was well developed, well nourished, weighed 176 pounds and showed no evidence of weight loss. He was afebrile. An enlarged tender liver was palpated. The liver edge was felt 12 cm. below the right costal margin in the right midclavicular line and could be followed into the left upper quadrant. There was no enlargement of the spleen or lymph nodes. A routine blood count revealed 4,460,000 red blood cells per cu. mm. with 12.4 gm. of hemoglobin. There were 20,650 white blood cells per cu. mm., with 48 per cent neutrophils, 16 per cent lymphocytes, 4 per cent monocytes and 32 per cent eosinophils. Because of the hepatomegaly and leukocytosis with eosinophilia, the patient was admitted to the hospital for diagnostic study.

Many laboratory tests and various procedures were carried out to determine the cause of the eosinophilia and hepatomegaly. Table 1 shows the results of the many blood counts, the white blood cell counts ranging from 20,650 to 64,850 per cu. mm.,

Table I

Results of Blood Counts

Date	RBC/cu. mm.	WBC/cu. mm.	% Eosinophils
5/25/49	4.46	20,650	32
5/26/49	4.34	28,650	33
5/28/49	—	28,500	24
6/3/49	3.64	29,950	26
6/6/49	3.76	28,450	35
6/15/49	3.98	44,550	21
6/20/49	—	64,850	34
6/29/49	3.46	46,400	23

with eosinophilia from 21 per cent to 35 per cent. In the various examinations of the blood smears, the eosinophils were all mature. Many urinalyses revealed no significant abnormality. Liver function tests resulted in the following: icterus index of 12 units, bromsulfalein retention of 50 per cent at 45 minutes, prothrombin time 94 per cent to 100 per cent (three determinations), serum albumin 3.3 gm. per cent, serum globulin 2.7 gm. per cent, cephalin flocculation test 1 plus, thymol turbidity 2.3 units, thymol flocculation negative. Several examinations and cultures of feces were negative for ova and parasites. On two occasions the feces were positive for blood with the guaiac reagent.

Two bone marrow aspirations were done and the hematologist reported normal maturation, with excessive production of eosinophils but a normal number of megakaryocytes and mature red and white cells. Immature forms of eosinophils were not seen in the marrow examinations. Smears of the peripheral blood revealed no immature cell form and were unusual only in the number of mature eosinophils.

A liver biopsy was performed and the histologic report from Tracy B. Mallory, Massachusetts General Hospital, follows:

"The liver is essentially normal except for two presumably unconnected findings: (1) moderate fat infiltration; (2) the presence of many sharply focal inflammatory lesions composed predominantly of eosinophils with only occasional histiocytes and lymphocytes. No parasites can be identified. The lesions are not connected with bile ducts or blood vessels and appear to be scattered indiscriminately without lobular orientation."

Various roentgen examinations were performed. The lung fields and heart were normal. An upper gastrointestinal barium study revealed only a small reducible hiatus hernia. The barium enema revealed a smooth area of narrowing in the distal sigmoid, thought to be caused by spasm. The ascending colon was incompletely filled because of retention of feces. Reëxamination was requested in two weeks but was not done because of the patient's condition at that time. A suspicious rectal lesion in the ampulla was biopsied but the microscopic examination showed essentially normal rectal tissue.

On the basis of the findings described, many diagnoses were entertained but confirmation was not forthcoming. The liver biopsy was consistent with early alcoholic cirrhosis, and a parasitic infestation, such as trichinosis or schistosomiasis, which seemed unlikely. Eosinophilic leukemia was not supported by the bone marrow findings. The most likely diagnosis, because of the hepatomegaly, seemed to be a metastatic carcinoma, site and type of origin undetermined.

The course in the hospital was quite interesting. For the first three weeks, the patient had no specific complaints except occasional epigastric discomfort. However, in the fourth week there was rapid deterioration in his condition. There were marked anorexia, weakness, nausea and occasional vomiting. The patient was afebrile during the whole course, except for the last three days before death, when an elevation to a maximum of 103° F. was recorded. Evidence of hepatic insufficiency appeared quite rapidly, in the course of three days, the patient becoming comatose and dying on July 1, 1949, 35 days after first being seen.

Postmortem examination was performed three hours after death. The liver weighed 2,000 gm., and there was diffuse infiltration by firm white large nodules, some with central softening and umbilication. The left lobe of the liver appeared more involved than the right in the neoplastic process. Examination of the colon revealed four polyps in the descending colon, two polyps in the transverse colon, and a polypoid tumor mass at the hepatic flexure, with marked thickening of 80 per cent of the wall without occlusion. All the mesenteric lymph nodes revealed hard white metastatic lesions.

Microscopic examination of the tumor revealed a typical carcinoma of the colon.

No unusual excess of eosinophils was noted locally in the primary tumor. There were metastases in the regional lymph nodes, lungs, omentum, spleen and liver characteristic of carcinoma of the colon. The adrenal glands were not involved by metastases. On histologic study of the liver, in addition to the areas of metastasis there were found necrosis and abscess formation with marked pericholangitis and bile stasis. The pathologist remarked that the type cell in the inflammatory areas in the liver was primarily eosinophilic, a most unusual finding. The bone marrow showed marked hyperplasia of the white cell series, the predominant cell being the eosinophilic myelocyte.

In summary, a 52 year old white male showed epigastric pain, hepatomegaly, leukocytosis and marked eosinophilia. On admission he did not appear or feel very sick, but in the course of 35 days he died in hepatic coma caused by carcinomatosis. The singular feature of this case of carcinoma of the colon with widespread metastasis was the occurrence of a leukemoid hematologic response with very marked eosinophilia. The bone marrow showed eosinophilic hyperplasia, and there was marked infiltration of the liver with eosinophils. The rapidly fatal outcome is noteworthy.

In retrospect, it is believed that a repeated liver biopsy might have given a more definitive antemortem diagnosis. Experience with needle biopsy of the liver has demonstrated that equivocal histologic findings in one specimen may be clarified by another biopsy. In marked hepatomegaly, it is safe to biopsy the left lobe of the liver (which in the present case was very prominent).

Discussion

The association of the eosinophil with the reaction to foreign protein and allergic disorders has long been well known. Rebuck [6] and Samter [7] have recently reviewed the varied functions of the eosinophilic leukocyte. Samter demonstrated the difficulty in the experimental study of the eosinophilic response and reviewed the disagreement as to site of origin of the eosinophil. He also strongly recommended absolute eosinophil counts rather than the less accurate percentage counts obtained in examination of routine blood smears. It is unfortunate that, in the case presented, absolute eosinophil counts were not obtained. More recently, pituitary adrenocorticotropic hormone has been shown to cause a fall in the circulating eosinophils in the normal human being.[8] However, there has been no completely satisfactory explanation for the occasional occurrence of eosinophilia with malignant tumors.

The significance of an increased number of eosinophilic cells in bone marrow smears, a finding present in our case, has been recently discussed by Lanier.[9] In 32 cases of metastatic cancer, she reported finding an increased number of eosinophilic cells in 46.9 per cent of the cases. She concluded that such an increase, in the absence of other known causes for eosinophilia, such as dermatitis, asthma or other allergic states, should suggest the presence of a malignant tumor which has metastasized.

Gill [10] advanced the tentative idea that local tissue eosinophilia in carcinoma of the cervix was a good prognostic sign and indicated better than usual resistance to the advance of the neoplasm. He based this on a study of 309 cases of epidermoid carcinoma of the cervix. In 7.7 per cent of these tissue examinations, local eosinophilia was outstanding. The clinical course in this group seemed somewhat better than in those without local eosinophilia, but it was a small group for which statistical significance and validity were not demonstrated. The author hoped that long term observation would confirm the value of local eosinophilia as a fa-

vorable prognostic sign in this cancer. Unfortunately, blood eosinophil studies were not mentioned by Gill. It has been demonstrated that the prognosis is extremely poor in cases of malignancy with blood eosinophilia, a conclusion in marked contradistinction to that of Gill.

Biggart [11] also presented a study of tissue eosinophilia in malignant disease. He found this phenomenon present in a varied list of entities, including chronic gastric ulcer, appendicitis, epithelioma of the hand, and carcinoma of the thyroid and gastrointestinal tract. He stated that every neoplasm of the gastrointestinal tract showed a local eosinophilia regardless of the presence or absence of an inflammatory reaction. It was his contention that local tissue eosinophilia occurred at the expense of the circulating eosinophils; in effect, the tissue eosinophil was an emigrated blood eosinophil. However, in Biggart's presentation no correlation of local tissue eosinophilia and blood eosinophilia was studied specifically or proposed.

In the case presented above, aside from the blood, local eosinophilia was marked in the liver parenchyma and liver metastases but not in the original tumor. Small areas of necrosis were noted only in the liver tumor nodules. In 10 of the cases with blood eosinophilia presented by Isaacson and Rapoport,[2] specific mention was made of both local tissue eosinophilia and tissue necrosis in the primary tumor. In only two of the cases was there local tissue eosinophilia. Necrosis of the tumor was present in six of the 10 cases. Of the two tumors with local tissue eosinophilia, one showed necrosis and the other did not. Thus, in these cases, there seems to be no correlation of tissue necrosis and local eosinophilia. There is also apparently no direct correlation of the blood eosinophilia either with tissue necrosis or local eosinophilia, since blood eosinophilia has been found in malignant growths with the absence of one or both of these factors.

In the case presented, the histologic findings in the parenchyma of the sections of liver uninvolved by metastasis are somewhat similar to the liver biopsy in the case of familial eosinophilia described by Atmar.[12] In his case, a 25 year old Mexican female, the white blood cell counts varied from 27,100 to 30,000 per cu. mm., with 58 to 70 per cent eosinophilia. The patient did not have hepatomegaly. Of four siblings, two brothers and one sister also showed marked eosinophilia. Stool examinations in the whole family did not demonstrate parasites or ova. During a laparotomy for an umbilical hernia, a liver biopsy was obtained. The surface of the liver had many grayish white areas, 0.5 to 1.0 cm. in diameter. Histologic examination revealed a dense infiltration of the hepatic parenchyma with eosinophilic leukocytes, resulting in complete replacement of hepatic cells in some areas. These histologic findings are quite similar to those reported in the liver biopsy of our patient. Yet, in the case of Atmar's patient, the eosinophilia was apparently a benign familial trait.

Most writers admit that the cause of eosinophilia in malignant tumors is obscure. Yet it appears to be the consensus that necrosis of the primary tumor or of its metastases is in some way connected with the occurrence of eosinophilia. Special conditions of tumor necrosis, with liberation of protein degenerative products to which the individual has, perhaps, a strong allergic susceptibility, have been invoked to explain the eosinophilia. It would appear that satisfactory substantiation of the theories involving tumor necrosis has not been presented.

Analysis of the reported cases with sufficient data referable to tissue necrosis lends only partial support to this hypothesis. It is to be noted that the liver is involved by metastatic lesions in a majority of the cases but not in all. The part the liver plays in the occurrence of eosinophilia is also not clear.

Summary

A review of the occurrence of marked eosinophilia with malignant tumors, with a case report has been presented. It would appear that eosinophilia is an extremely poor prognostic sign in association with cancer. In many of the cases reported, there have been hepatic metastases. The explanation of the occurrence of eosinophilia in cancer remains obscure.

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EPIDEMIC PAROTITIS COMPLICATED BY PERICARDITIS AND SEROSITIS *

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Though epidemic parotitis is a generalized infection, and thereby capable of affecting the various organ systems, cardiac complications are unusual. That the heart could be implicated in mumps was first suggested in 1918 by Pujol.[7] This author, during a nine-month period, observed 450 cases of mumps, 12 of

* Received for publication June 18, 1949.

whom had circulatory disturbances. Nine of these had associated heart disease, attributable to different etiologies. The remaining three, because of the development of substernal pain and dyspnea during the convalescent period, were believed to have myocarditis secondary to their mumps infection. These initial clinical observations, unfortunately, could not be corroborated electrocardiographically. Additional evidence of myocardial involvement secondary to mumps was contributed by Manca,[6] who concluded from postmortem observations that "the mumps virus can attack the heart, and the lesion consists of an acute interstitial myocarditis, especially characterized by a fibrinous exudate, which differentiates it from other forms of myocarditis and may be considered a peculiarity of this infection."

It was not until 1944, however, that the clinical and pathologic observations were confirmed by electrocardiographic evidence of myocardial involvement. In a group of 15 soldiers on whom survey electrocardiograms were done, Wendkos and Noll [11] reported one instance of acute myocarditis, as evidenced by first degree heart block, manifested by prolongation of the PR interval to 0.28 second. Rosenberg [8, 9] in 1945 and Felknor and Pullen [2] in 1946 contributed additional cases of myocarditis complicating mumps. Rosenberg's initial series included two cases of complete heart block occurring two and 17 days after the onset of parotid swelling, and manifested by retrosternal pain. These observations stimulated that author to do electrocardiographic studies on a consecutive series of 104 adults with mumps. In 15.4 per cent significant electrocardiographic abnormalities were noted, consisting of diphasic or inverted P waves in one or more leads (25 per cent), increased PR interval (12.5 per cent), inverted QRS in CF_4 (6.2 per cent), elevated ST_4 (12.5 per cent), depression of ST_2 and ST_3 (6.2 per cent). T wave alterations were noted in all 16 patients, and in two, two or more leads were involved. In all but one, the electrocardiographic changes developed between the fifth and tenth days, returning to normal, in 14 instances, in two to 35 days. Of the 16 patients so affected, only four experienced symptoms of precordial pain. Felknor and Pullen's case demonstrated evidence of a "subacute pericarditis and myocarditis" with slight slurring of QRS, slight elevation of $ST_{1, 2, 3}$, low T waves, and inverted T_1 and T_4.

Case Report

A 29 year old white male was admitted on July 23, 1948, with the following pertinent history:

The patient was entirely well until July 16, 1948, eight days prior to admission, at which time he noted the onset of left parotid swelling. This was associated with dysphagia, and pain at the site of the swelling with mastication. A diagnosis of parotitis was made and the patient confined to bed at home. Salicylates constituted the sole therapy, on which regimen he progressively improved, with subsidence of the swelling, until July 22. At that time he experienced the onset of cough, paroxysmal in character, productive of sparse amounts of mucoid sputum and accompanied by a dull ache in the left lower anterior chest. Concomitantly, the right testicle became enlarged and exquisitely painful and tender. Associated with this complaint, the patient experienced alternate fever and chilly sensations. These complaints persisted until the time of admission.

Physical examination revealed the patient to be well developed and well nourished, complaining of testicular pain but in no acute distress. Temperature 102.6° F.; blood

pressure 128 mm. Hg systolic and 68 mm. diastolic. Examination of the eyes, ears and nose was unremarkable. The fundi were normal, the pharynx was clear and the tonsils were benign. The inferior pole of the left parotid gland was palpable at the angle of the jaw. It was firm, smooth and minimally tender. The left Stensen's duct was patulous and, on massage of the gland, a thin, milky discharge was noted to escape from the ostium of the duct. Examination of the lungs revealed them to be resonant to percussion. Over both lower lobes, the right greater than the left, were noted occasional showers of crackling inspiratory râles of the crepitant-subcrepitant variety. The heart was normal in size, configuration, rate and rhythm. There were no murmurs or thrills. The rhythm was regular and sinus. A_2 was louder than P_2. The abdomen was soft and nontender. No masses or organ edges were palpable. Examination of the genitalia revealed the left testis and epididymis to be enlarged to three to four times normal size. These were firm and markedly tender, and did not transilluminate light. The extremities were normal, and neurologic examination was physiologic.

Laboratory data at the time of admission revealed red blood cells of 4.8 million, with 85 per cent hemoglobin, white blood cells 9,100 with 64 per cent polymorphonuclears, 34 per cent lymphocytes, 1 per cent monocytes, and 1 per cent eosinophils. Urinalysis revealed a specific gravity of 1.027; it was negative for sugar, albumin and abnormal formed elements. Serologic test for syphilis negative. Serum amylase 20 units (normal 0 to 64 units). Chest roentgenogram revealed both lung fields to be clear, and the cardiac silhouette normal. Throat culture revealed *Neisseria catarrhalis*, *Micrococcus flavus*, and *Staphylococcus aureus*. Antistreptolysin titer was negative.

Therapy consisted of complete bed-rest, the use of a suspensory and the application of ice bags to the scrotum. Codeine sulfate was given for the relief of pain, and aspirin administered in 0.65 gm. doses every four hours for fever. On July 25, one day after admission, at which time the temperature was fluctuating between 100 and 103° F. the patient complained of weakness and generalized malaise. Chest pain was aggravated, testicular pain reduced. It was noted during the course of the day that the pulse was of small amplitude and poor quality. This finding was borne out by frequent examination. Examination of the heart revealed the organ to be of normal size, shape, rate and rhythm. Auscultation at the mitral area revealed the presence of a coarse, leather-like friction rub, high-pitched and occurring during systole. There was no diastolic alteration, and the rub was unaffected by respiratory excursions, and increased with apnea. Electrocardiogram taken at that time revealed the voltage to be low in standard leads, with inversion of T_1, T_2 and T_4. Sedimentation rate 28 mm. per hour (figure 1, column 1). Course by weeks was as follows:

By the third hospital day, the temperature had fallen to subnormal levels of 96 to 97° F., rising by the following day to normal levels, where it remained throughout the rest of the first hospital week. Coördinate changes in the pulse were noted. Following the appearance of the friction rub, the blood pressure fluctuated between 100 and 104 systolic and 70 and 80 diastolic. By the end of the first hospital week however, a normal pulse pressure had been attained, the systolic fluctuating between 110 and 130, and the diastolic between 68 and 80. Symptomatically the pain in the testicle gradually subsided, and the organ became of normal size and nontender. Further, the parotid swelling noted on admission similarly subsided during the course of the first hospital week. Cardiac fluoroscopy performed on the sixth hospital day revealed normal pulsations and no evidence of chamber enlargement. It was noted, however, that there was some accentuation of the right border of the cardiac silhouette in its lower aspects. A fibrotic strand was noted to emanate from this point to the anterior chest wall. This was also seen well on chest films, resulting in a slight tenting of the pericardium on the right anterior border of the heart (figure 3, A and B). Sedimentation rates fluctuated between 28 and 33 mm. per hour. Antistrepto-

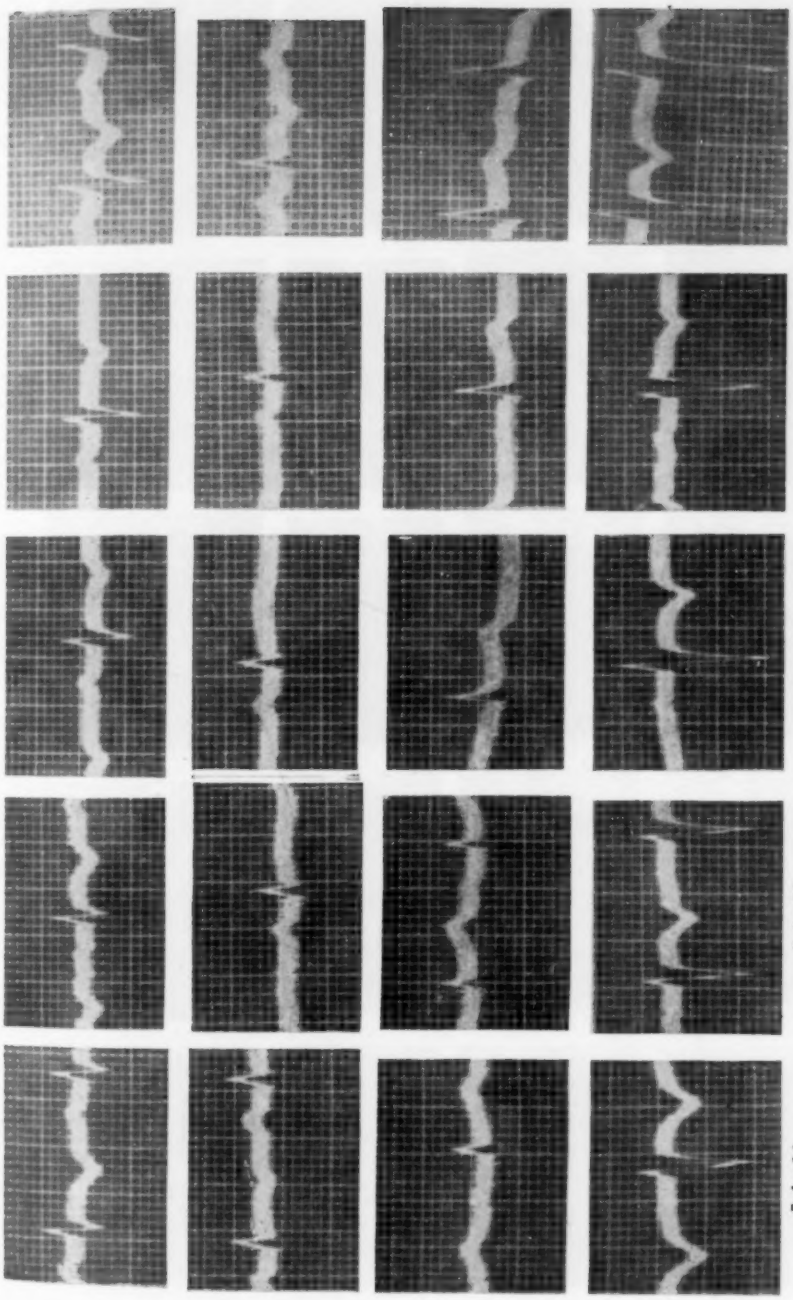


FIG 1.

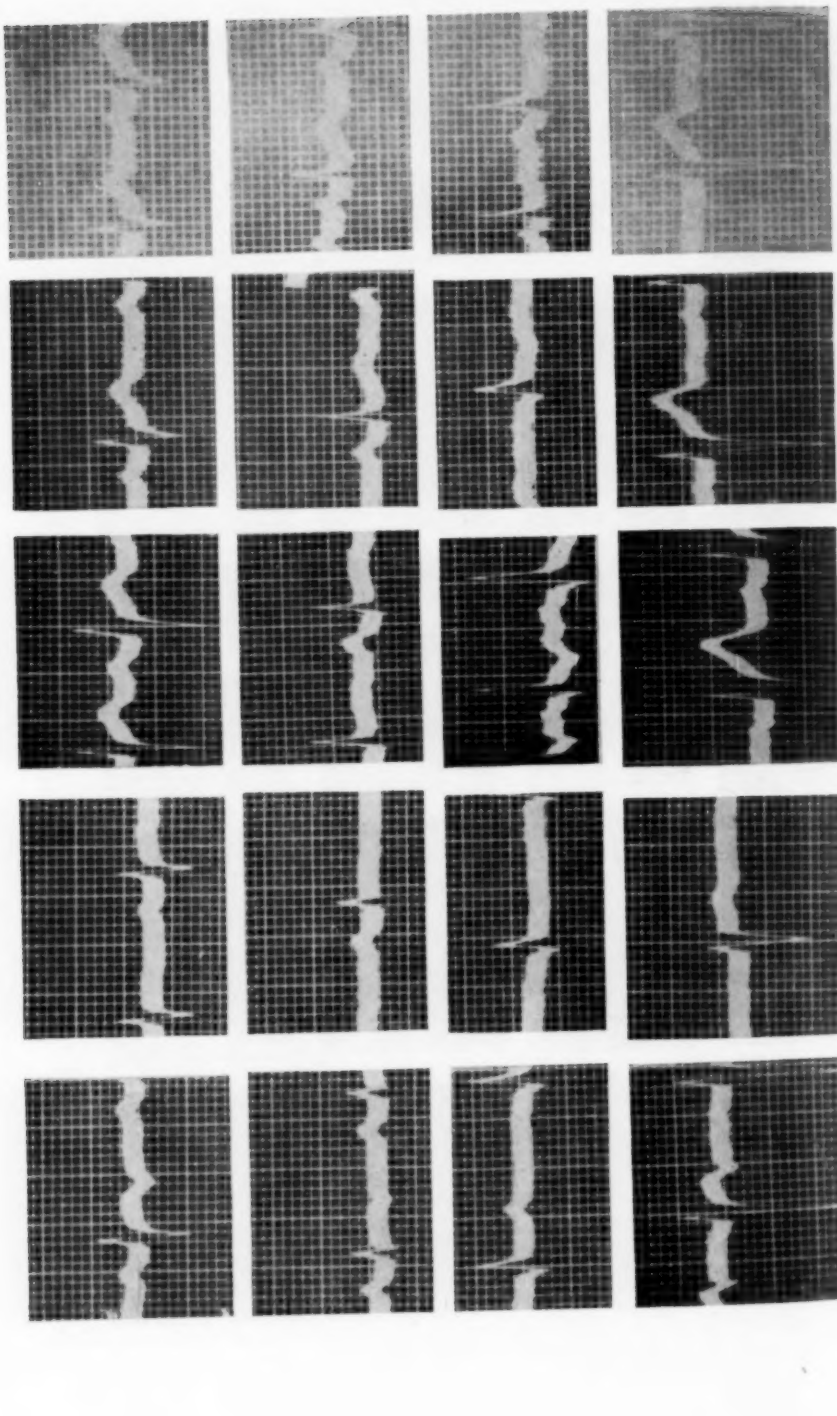


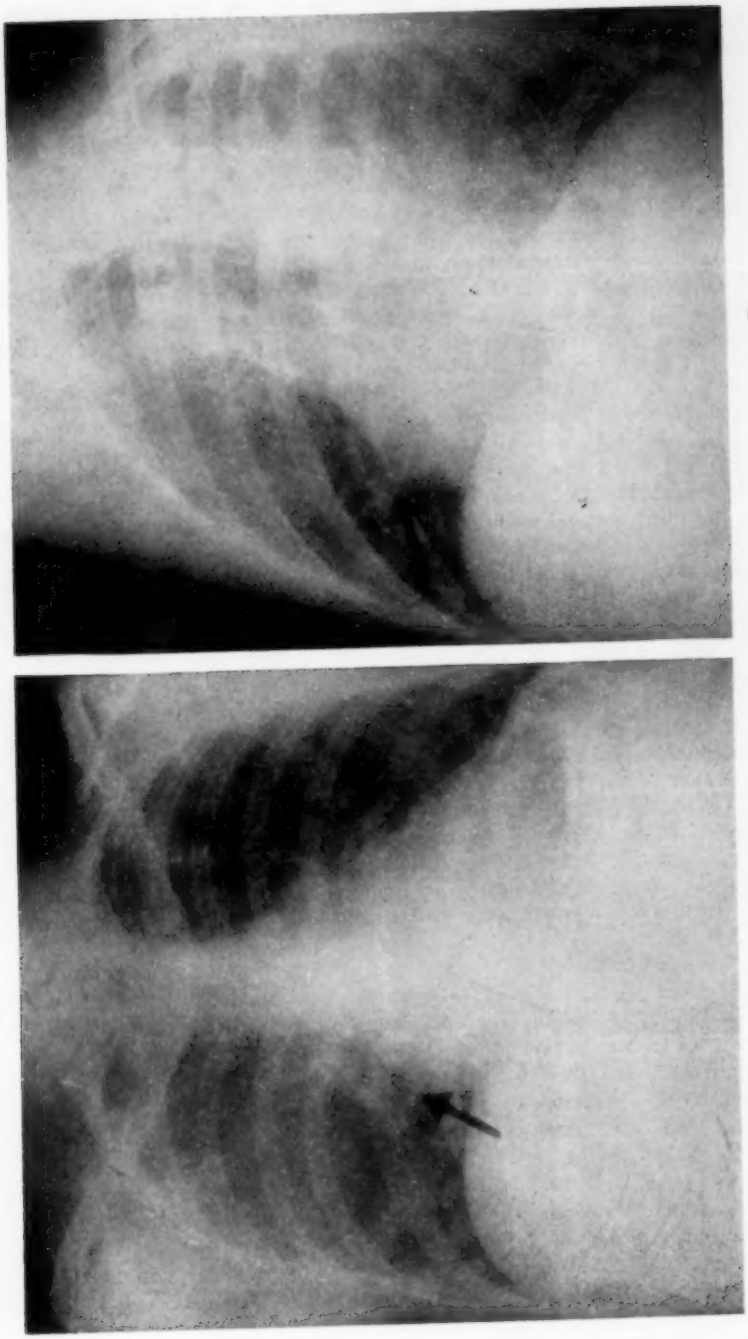
FIG. 2.

lysin titer remained negative. By the latter part of the first hospital week, the electrocardiogram was noted to have changed. T_2 became upright and of low voltage, and ST_2 became minimally elevated (figure 1, columns 3 and 4).

During the second hospital week, the patient remained afebrile with the exception of occasional rises to 99 or 99.2° F. Pulse and blood pressure remained normal. At the beginning of the second hospital week, the patient complained of pain in the left shoulder, associated with inability to abduct the arm or completely flex the extremity beyond 30 degrees. Examination revealed point tenderness of the glenohumeral articulation. No crepitus was noted. The joint was not erythematous, edematous or warm. There was limitation of both passive and active movement of the joint in abduction, circumduction and flexion. Intermittently throughout the second hospital week, pain of a similar character was experienced in the left shoulder, right shoulder and both wrist joints. Pain at all sites was aggravated by movement, and the only objective manifestation noted was tenderness. On one occasion, similar involvement of the left temporomandibular joint was noted, induced particularly by occlusion, and associated with a moderate degree of trismus. Sedimentation rate fluctuated between 32 and 36. Electrocardiograms revealed persistence of the findings of inversion of T_3 and T_4, as well as low voltage T_2. White blood cells fluctuated between 8,300 and 9,250, and the polymorphonuclears between 54 and 70 per cent. Roentgen-ray examination of the joints involved revealed no abnormalities.

During the third hospital week the temperature similarly remained normal, with the exception of one spike to 99.8° F. Blood pressure and pulse remained normal. Sedimentation rate fluctuated between 32 and 36. White blood cells fluctuated between 10,100 and 11,400, and the polymorphonuclears between 62 and 69 per cent. A report obtained at that time showed that the mumps complement fixation test was positive at diagnostic titers, while the antistreptolysin titer remained negative. Calcium 11 mg. per cent, phosphorus 4.35 mg. per cent, alkaline phosphatase 1.15 B. units. Arthralgic complaints as noted during the second week, limited to the shoulders, wrists and temporomandibular joints, persisted until the middle of the third hospital week. With the exception of these complaints, the patient experienced no symptoms. Frequent examination of the heart revealed no recurrence of the friction rub. (This had not been present, with the exception of the second hospital day.) During the third hospital week, the electrocardiogram again changed, in that T_3 again became inverted, while T_3 and T_4 became more deeply inverted, and the minimal ST segment elevation in Lead III persisted (figure 1, column 5). Therapy throughout the period of time that the arthralgia was experienced consisted of complete bed-rest, including the feeding and bathing of the patient, salicylates to the extent of 9.0 gm. of the sodium salt daily, and cold topical applications.

During the fourth hospital week, temperature, pulse and blood pressure were all within normal limits. Following the subsidence of the arthralgic complaints, there was no recurrence of similar symptoms. The patient was completely asymptomatic, experiencing no symptoms referable to any serous surface. For the latter part of the fourth hospital week, sedimentation rate gradually returned to normal limits, falling over a period of one week from 35 to 27 mm. per hour. Antistreptolysin titers remained normal. During the latter part of the fourth hospital week, the electrocardiogram was noted to revert toward normal, at first evidenced by T_4 becoming upright, and T_3 and T_2 less deeply inverted (figure 2, column 1). Later in the course of that week, T_3 became similarly upright. The patient remained symptom-free, his temperature, pulse and blood pressure remained within normal limits, and the sedimentation rate fluctuated between normal and minimally elevated levels of 25 to 26 mm. per hour. The electrocardiogram continued to reveal progressive return towards normal, with continued upright T_3, T_2, and T_4.



B

A

FIG. 3.

During the early part of the fifth hospital week the patient was slowly ambulated, as a result of which he experienced no ill effects, and manifested no alteration in the progressive return to normal of either the electrocardiogram (figure 2, column 2) or the sedimentation rate. Physical examination, after the subsidence of the arthralgia, remained unchanged.

The patient was discharged asymptomatic at the end of his sixth hospital week. Sedimentation rate, electrocardiogram (figure 2, column 3) and antistreptolysin titer remained normal. He was followed at weekly intervals for a period of three months, during which time he remained symptom-free; laboratory and electrocardiographic studies remained normal (figure 2, columns 4 and 5), and there was no recurrence of the symptoms of chest pain or arthralgia.

Discussion

Though chest pain has been noted as the outstanding symptom accompanying cardiac involvement in mumps,[2, 4, 7, 8, 9] the coexistence of a friction rub has never been reported previously to my knowledge. It may be surmised that the chest ache, noted by the patient on the day prior to admission, represented the symptomatic antecedent of the cardiac pathology. The character of the syndrome is comparable with that noted by Logue and Wendkos,[5] who reported benign pericarditis complicating upper respiratory infections, characterized by chest pain, transient friction rub, fever, elevation of the sedimentation rate and electrocardiographic alterations reflected in the ST segment and T waves.

Arthritis in the "true" sense, manifesting itself as the "red, hot, swollen" joint, has not been described in mumps. Painful joints, though unusual, have been previously noted.[10] It is likely that this represents an inflammation of serous surfaces of the same character as that evidenced by pericarditis, pleuritis or orchitis. It may be argued that the syndrome of pericarditis and arthritis represents a complicating condition of rheumatic origin, independent of and unrelated to the parotitis. That this is unlikely is evidenced by the absence of streptococci in the throat culture, the lack of objective or radiologic evidence of frank arthritis, and the repeatedly negative antistreptolysin titers. A similar hypothesis was postulated by Rosenberg [8] and refuted by that author for, except for one case, all patients with electrocardiographic changes reported by him had been participating in the program of continuous mass prophylaxis with sulfonamides.

Worthy of mention is the elevated sedimentation rate, which persisted until the resolution of electrocardiographic abnormalities. Though the most likely explanation for the rapid sedimentation rate and leukocytosis is the pericarditis and serositis, orchitis alone, as reported by Candel and his co-workers,[1] is associated with a marked increase in the sedimentation rate, which may persist for weeks after apparent recovery. That the sedimentation rate, in the case presented, increased from 28 mm. at the initiation of the complication to 36 mm. at its height is significant evidence of causal relationship.

Summary

1. A case is presented of epidemic parotitis, complicated by orchitis, pericarditis and serositis.

2. Electrocardiographic changes during the acute phase of the illness, during

convalescence and over a three month follow-up period are presented and described.

3. The literature to date relevant to cardiac complications in mumps is reviewed.

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TRANSIENT PERIODS OF CARDIAC ENLARGEMENT ASSOCIATED WITH HYPERSENSITIVITY TO DIFFERENT ETIOLOGIC AGENTS: REPORT OF A CASE*

By C. A. McKinlay, M.D., F.A.C.P., *Minneapolis, Minnesota*

The development in a young adult of abrupt enlargement of the cardiac silhouette, of signs of pericarditis and of left pleural effusion, occurring transiently in the course of serum sickness, was recently reported [1] by the writer. The findings were of particular interest because they were considered to be anaphylactic in origin. The occasion for the present report was the fortuitous occurrence in the same individual, at the end of convalescence from serum sickness, of pharyngitis and tonsillitis, which was followed, after a five-day interlude of normal temperature, by a second transient enlargement of the heart. Under close observation, circumstances produced an experimental disease controlled to the extent that, before both bouts of cardiac enlargement and abnormal signs, there was a normal base line of physical and serial roentgen-ray findings. The similarity of the two episodes, apparently due to two different etiologic agents, has stimulated consideration of the common pathogenic mechanism of hypersensitivity.

* Received for publication November 16, 1949.
From the Department of Internal Medicine, Northwestern Hospital.

Case Report

The patient was a 20 year old white male who, after 31 days of convalescence from serum sickness (previously reported [1]), developed sore throat, body aches and pyrexia. The fever of two days' duration (maximum of 101.2° F.) was associated with tachycardia (106 to 130) and signs of follicular tonsillitis and pharyngitis. The throat culture showed *Streptococcus viridans*. The patient developed a brief anxiety state, with headaches and vomiting which promptly subsided. The heart and central nervous system showed nothing abnormal.

On the sixth day after the temperature and pulse rate had become normal, the patient complained of a catching pain over the left anterior chest and precordium aggravated by deep respiration. Substernal pain occurred, aggravated by movements such as torsion of the chest or flexion of the neck. The nature of the pain suggested a pericardial origin. Pyrexia developed, reached a maximum of 102.6° F. and subsided to a sustained normal level after four days. Tachycardia (100 to 120) appeared with gallop rhythm. This disturbance of rhythm was repeatedly observed. There was lack of differentiation of heart tones. No murmur was heard at this stage. Leukocytosis of 13,800 developed, with 72 per cent neutrophils. At the same time the heterophil antibody reaction dropped to 1:8 from the 1:64 first noted with the

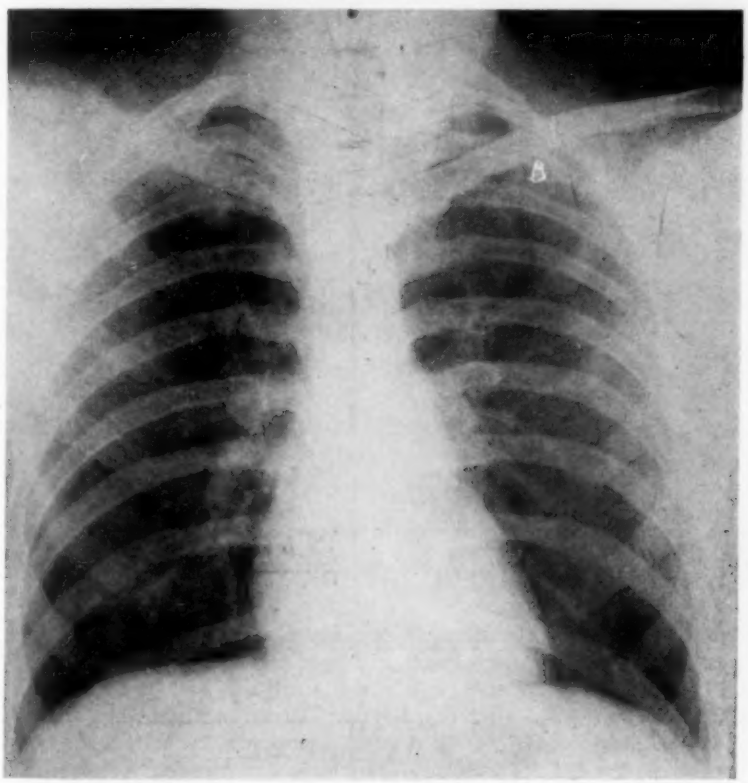

FIG. 1. Jan. 6, 1948. Normal cardiac area after first period of enlargement. (All films at 6 feet.)

serum sickness. Coincidentally, the sedimentation rate of erythrocytes per hour increased to a maximum of 114 mm. Blood cultures taken during the period of pyrexia showed no growth.

Most remarkable at the time of the occurrence of abnormal cardiac signs was the marked increase in the cardiac silhouette—to a transverse diameter of 15.1 cm. from the previous normal of 11.7 cm. (figures 1, 2 and 3). The outline did not suggest pericardial effusion. There was a question of slight pleural thickening. Definite decrease in the cardiac area was noted nine days later, with return to the previous

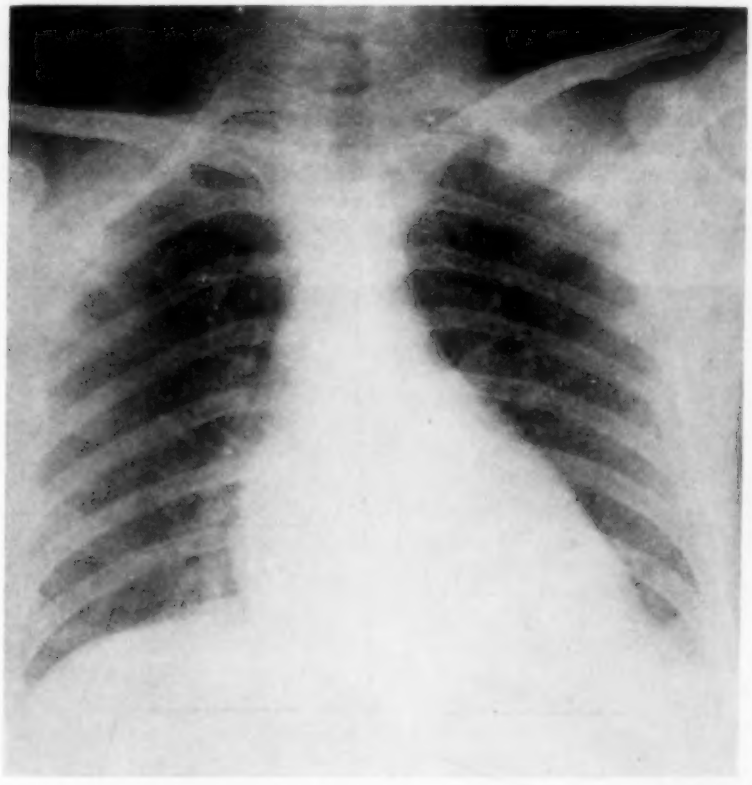

FIG. 2. Feb. 7, 1948. Marked cardiac enlargement. Pericardial effusion was not suggested. Haziness at the left base suggests a small pleural effusion. There is a small infiltration at the right base in region of the costophrenic angle.

normal area on a six-foot film taken 17 days later. Simultaneously with the increase in the cardiac area, the electrocardiogram showed minor changes suggesting an active process; T_1 and T_2 were positive but of small amplitude, and T_4 (CF_4) was diphasic (figure 4). Thereafter the electrocardiogram showed persistent negativity of the T_4 wave. As the temperature became normal, tachycardia subsided and symptomatic improvement supervened. The clinical diagnosis was transient pericarditis, pleurisy and cardiac dilatation. During the succeeding 12 months the patient has been in good health. The cardiac area has remained within the initial normal limits.

Discussion

In contrast to the precipitation of the first episode of cardiac enlargement, pericarditis and pleuritis by the injection of tetanus antitoxin, the second was initiated by pharyngitis. Fever, leukocytosis and increased sedimentation rate of erythrocytes were followed by a latent afebrile period. On the sixth day after the temperature and pulse rate had returned to normal, abnormal cardiac signs developed

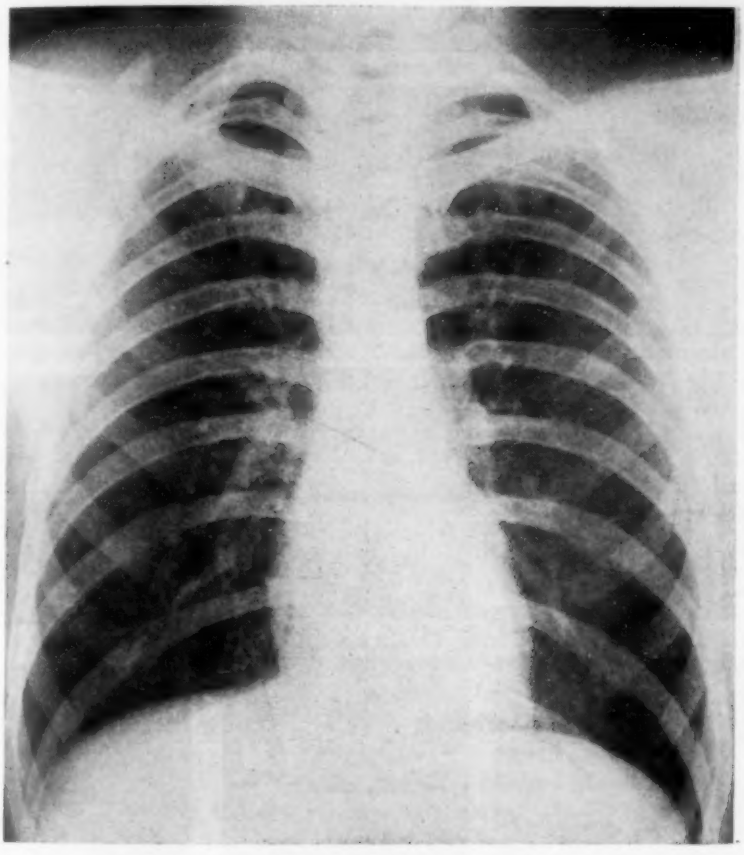

Fig. 3. Mar. 5, 1948. Normal cardiac area and lung fields. Definite decrease in the size of the cardiac shadow had also been noted Feb. 16, 1948, with normal lung fields.

similar to those of the first episode. The decrease in titer of the heterophil antibody reaction to normal limits (1 to 8) made the previous elevation (1 to 64), noted during serum sickness, more significant in support of this diagnosis. This test had been inadvertently delayed until late in the course of serum sickness. Increased cardiac silhouette was readily demonstrated in both bouts, because before and after each a base line of normal cardiac findings was recorded. The fleeting nature of the abnormal cardiac signs was similar to many hypersensitive reactions.

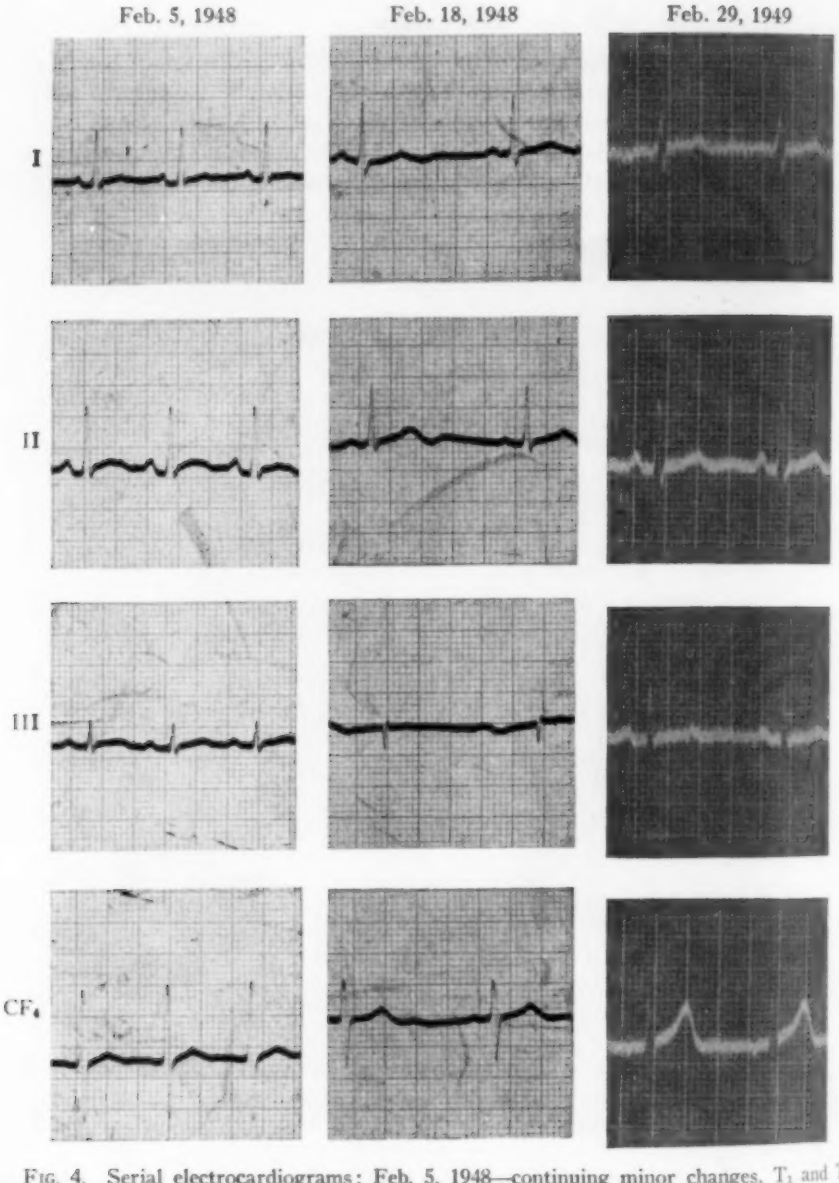

FIG. 4. Serial electrocardiograms: Feb. 5, 1948—continuing minor changes, T_1 and T_2 flatter, ST_2 more rounded, T_2 diphasic; Feb. 18, 1948—ST_2 is less elevated, T_2 diphasic, and pattern is changing toward normal; Feb. 29, 1949—within normal limits.

No evidence of deficiency disease of any type was encountered. Cardiac dilatation is presumed to account chiefly for the enlargement of the heart.

Experimental evidence of Vaubel,[2] Hall and Anderson,[3] Rich [4] and Moore and associates [5] indicates that animals subjected to sublethal anaphylactic shock develop cardiac lesions similar to those seen in human rheumatic fever. Swift [6]

had suggested that in rheumatic fever the synovial membranes and other tissues were sensitized during the latent period, with a response similar to that after an injection of a foreign protein (horse serum). Focal collagen and vascular damage basically the same as that of acute rheumatic fever have resulted from focal anaphylactic reactions. The occurrence of myocarditis and valvulitis due to serum sickness has been well established experimentally. The relation of anaphylactic hypersensitivity to periarteritis nodosa has been established. Acute rheumatic fever presents a wide variety of phenomena known to occur also in the anaphylactic reaction of serum sickness. Common findings consist of cutaneous lesions (including urticaria, purpura and erythema), migratory arthritis tending to be relieved by salicylates, focal degeneration of collagen, tissue eosinophilia, vascular lesions of the erythema nodosum type, myocarditis and valvulitis. Migratory pneumonitis has also been identified as an anaphylactic phenomenon.

Wadsworth and Brown [7] report a case of carditis which followed the injection of tetanus antitoxin and subsequent accelerated serum sickness. Fox and Messeloff [8] noted electrocardiographic changes in a case under similar circumstances. Lyon [9] reported a case of allergic myocarditis following 14 injections of anti-rabic vaccine, the diagnosis supported by clinical and electrocardiographic evidence. This author suggests that myocarditis often may not be the result of infection, that the way in which the organism and heart muscle react may have a decisive part in the pathologic mechanism. Mathieu and Hadot [10] report two cases of accelerated serum sickness following injection of tentanus antitoxin, with electrocardiographic evidence of posterior myocardial infarction in one and with angina pectoris in the other. An anaphylactic reaction of the coronary arteries was implicated.

Of distinct interest are the four cases in children reported by Storey [11] which had in common the development of polyarthritis, fever, accelerated sedimentation rate and carditis (judged only by clinical findings) following injection of foreign serum. In three cases, serum sickness occurred in the interval between the serum injection and the discovery of carditis. The possibility of the occurrence of rheumatic fever with coincidental serum sickness was discussed, as well as the possible reactivation of rheumatic fever by protein shock. Storey suggests the possibility that in the last two cases there was no preceding infection and no true rheumatic fever, but that there was an antigen-antibody reaction initiated by the injection of tetanus antitoxin and that this produced an illness so closely simulating rheumatic fever, even to the extent of carditis, that it was impossible clinically to differentiate the two conditions. Clark [12] has described, in serum sickness in man, diffuse infiltration between the heart muscle fibers. A recent report [13] of the occurrence of abnormal electrocardiograms taken serially in 61 of 93 cases of diphtheria treated with foreign serum might suggest the possibility of hypersensitivity as an occasional factor. Ratner [14] states that the physician who reported his own case of pericarditis with effusion subsequent to the therapeutic use of diphtheria antitoxin, was hale and hearty 34 years later at the age of 63. Rantz, Boisvert and Spink,[15] from a study of 1,500 cases in the Army Corps, considered that rheumatic fever is invariably induced with group A hemolytic streptococcus, that during the silent period immune mechanisms are set in motion, and that an increased antistreptolysin titer is almost constantly observed. The clinical manifestations of varying severity make their appearance in the synovial membranes and other connective tissues and structures involved.

Fully realizing that the phenomena recorded in this article are clinical, this author believes that the physical, electrocardiographic and hematologic findings give support to the view that hypersensitivity was the common pathogenic mechanism and, due to it, conditions favorable to cardiac dilatation or enlargement occurred. Clinical evidence, including the type of pain, the abnormal physical signs and electrocardiographic changes, indicated that pericarditis and myocardial abnormality occurred. Actual edema of cardiac structures has been postulated by others in similar conditions. It is emphasized that the conditions reported created a clinical experiment controlled to the extent that before, during and after both transient bouts of cardiac enlargement there was a serial roentgen-ray record of the cardiac silhouette as well as clinical observation in the hospital. As to the heart, the fleeting abnormal signs in the second period which followed pharyngitis varied in no significant way from those in the first period of frank serum sickness. The clinical course of the development of hypersensitivity is the sequence of an etiologic agent (foreign serum, bacterial products, chemical) acting as an antigen, of a variable latent period of development of antibody and hypersensitivity, and of the hypersensitive response of some tissue or organ. The similarity of the course of events in the case reported to those in acute rheumatic fever is believed to support the concept of the pathogenesis of rheumatic fever as a tissue injury of a characteristic type by an anaphylactic reaction rather than by a specific etiologic agent.

Conclusions

A case is reported in which a second similar and transient period of cardiac enlargement occurred within one month of recovery from the first. Clinical evidence of pericarditis and myocardial abnormality was present in both episodes. The first period was quite frankly anaphylactic in nature, and the second followed pharyngitis and a latent afebrile phase. The etiologic agent in the first period appeared to be the injection of tetanus antitoxin and, in the second, pharyngitis, probably streptococcic. The similarity of the abnormal cardiac findings, and of the clinical course in the two periods suggests the common factor of hypersensitivity of the tissues to foreign proteins (tetanus antitoxin and bacterial products) as the pathogenic mechanism. The laboratory data also give support to the above concept.

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EOSINOPHILIC GRANULOMA OF RIB*

By David R. Weir, M.D., *Cleveland, Ohio*

Previous to 1940, eosinophilic granuloma of bone had not been recognized as a definite clinical entity. Since then over 50 cases have been reported, and a number of reviews of the subject have appeared in the recent literature.[1, 2, 3] Clinically and radiographically, eosinophilic granuloma may simulate a wide variety of bone diseases, ranging from simple cyst[4] to apparent malignant bone destruction such as existed in the case reported here. Although follow-up studies on most of the reported cases are necessarily incomplete, it is probable that the lesion usually is essentially benign and may be eradicated by surgical excision, curettage or roentgen-ray therapy. It is important to differentiate it from malignant bone disease.

Case Report

In June, 1948, a 38 year old white man began to have attacks of moderately severe right-sided chest pain lasting two to three hours. There was no history of cough, dyspnea, fever, weight loss, malaise or trauma. Physical examination on July 7 showed moderate tenderness over the right fifth rib in the anterior axillary line. With rest and the application of hot compresses the pain disappeared. Several weeks later it recurred and by the end of August had become persistent, involving the lateral chest wall in the region of the fifth rib. Nine weeks after the onset of the pain, radiographic studies were done. These demonstrated an area of osteolysis measuring about 6 cm. in length in the posterior arc of the right fifth rib. There was evidence of a pathologic fracture and some attempt at healing (figure 1). Films of the other ribs, skull, entire spine and pelvis failed to reveal other lesions. Intravenous pyelograms were normal. The differential diagnosis included metastatic carcinoma, bone sarcoma, isolated myeloma, lymphoma and eosinophilic granuloma.

* Received for publication June 14, 1949.
From the Department of Medicine, University Hospitals of Cleveland, Ohio.

The patient was admitted to the Lakeside Hospital for further study. Except for the tenderness in the right lateral chest wall, the physical examination was entirely normal. There was no enlargement of liver, spleen or lymph nodes. The temperature, pulse and respirations were normal. The blood pressure was 128 mm. Hg systolic and 78 mm. diastolic.

The urine had a specific gravity of 1.015, did not contain sugar or albumin, and showed no cellular elements or casts in the sediment. Three examinations for Bence-

FIG. 1. The roentgen-ray appearance of the lesion.

Jones protein were negative. The red blood cell count was 5,020,000, the hemoglobin 100 per cent. The white blood cell count was 8,150 and the differential count showed 57 per cent polymorphonuclears, 30 per cent lymphocytes, 9 per cent monocytes and 4 per cent eosinophils. The total plasma protein was 6.4 gm. per 100 c.c. albumin 4.8, globulin 1.6. The serum calcium was 9.7 mg. per 100 c.c., the phosphorus 3.9. Alkaline phosphatase was 3.4 units. Aspirated sternal marrow had a normal myeloid-erythroid content and normal nucleated cell count. The marrow differential count was also normal. The ratio of granulocytes to nucleated red

elements was 2:1, eosinophils were not increased above normal, and only rare plasma cells were seen.

On the fourth hospital day, resection of the rib was carried out by Dr. Frederick Mautz. The rib was disarticulated from the vertebral body and costochondral junction, and the intercostal muscles adjacent to the lesion were removed with the specimen. Convalescence from the operation was uneventful.

Pathologic Findings: The fresh specimen consisted of a complete rib measuring 30 cm. in length. (See figure 2.) In the region of the angle the bone was thickened but elsewhere was of normal contour. On section, widening of the medullary cavity was present for a distance of 3 cm. near the angle. In this area it measured 1 cm. in width, as compared to 0.5 cm. in the uninvolved portion. The cortex enclosing the widened area was thinned but everywhere appeared to be grossly intact. In the widened area, normal red marrow was replaced by yellowish-gray tissue, and this tissue extended for a few centimeters into the unexpanded portions of the rib, where

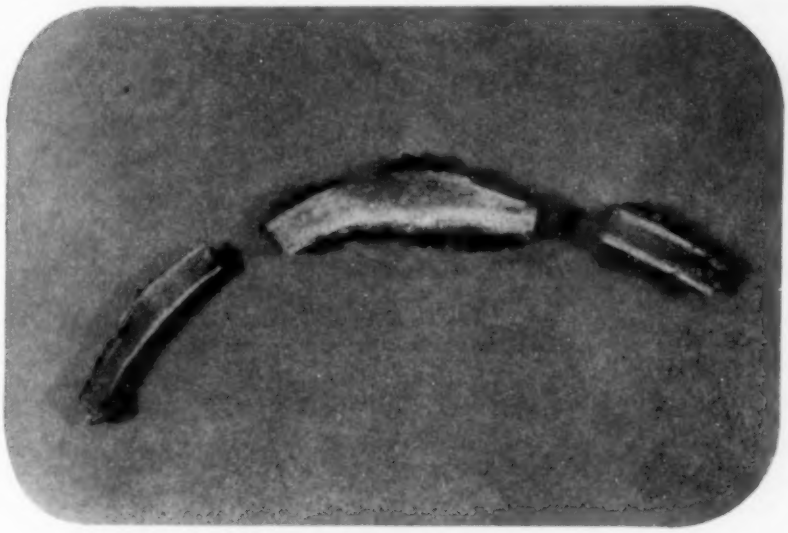

FIG. 2. The gross appearance of the lesion.

it merged into normal red marrow without a sharp line of demarcation. Microscopic sections of the lesion revealed loose connective tissue, including many small capillaries. Scattered through all sections were varying numbers of mature eosinophils. Also included were moderate numbers of mononuclear cells having poorly defined acidophilic cytoplasm and large round or oval, pale-staining nuclei with finely granular chromatin. The cortex was composed of bony trabeculae of variable size and shape, many of them lined with osteoblasts. Among the trabeculae were fragments of cartilage of irregular shape which, in places, merged with new bone. The pathologic diagnosis was eosinophilic granuloma of bone with osteogenesis consistent with healing fracture.

Five months after operation the patient was well and had no complaints. Roentgenograms of the right ribs were normal except for the absence of the fifth. Urine, sedimentation rate, hemoglobin, white blood count and smear were normal. Eight months after operation the patient was symptom-free and the physical examination was normal.

Discussion

The alarming roentgen-ray appearance of this lesion decided us to do radical excision in the hope of curing the patient if the process were malignant. Convalescence was uneventful and there is no residual disability. We feel that excision, if it can be carried out, is the treatment of choice. For lesions that cannot be excised, curettage or roentgen-ray therapy or both are indicated. At present there is little or no evidence in the literature to indicate that solitary lesions recur. A more generalized form of the disease exists involving lymph nodes and the reticuloendothelial system as well as bone. Morphologically, a similarity exists to Letterer-Siwe's disease and Hand-Schüller-Christian disease. Clinically it behaves not unlike lymphoma as to spread, involvement of nodes and response to radiation therapy. Whether this entity is identical with that causing the solitary lesions of bone remains to be proved. It seems likely that they differ, particularly as to prognosis.

Summary

A case is reported of solitary eosinophilic granuloma of rib simulating malignant bone disease.

Treatment was by radical excision.

The prognosis is believed to be excellent.

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BLOOD CELL CHANGES IN LEUKEMIA DURING AMINOPTERIN THERAPY *

By Raphael Isaacs, M.A., M.D., F.A.C.P., and Ralph W. Trimmer, M.D., F.A.C.P., *Chicago, Illinois*

The use of "anti-folic acid" preparations in the treatment of leukemia, as described by Farber, Diamond, Mercer, Sylvester and Wolf,[1] has made possible the study of the blood of patients with induced "folic acid deficiency." As folic acid appears to stimulate the maturation of "proerythroblasts" (megaloblasts in pernicious anemia), the absence of this substance should be associated with a delay in the maturation of these cells. Since the red blood cells develop their "size," at this stage, they become larger if delayed too long at this period.

* Received for publication March 4, 1950.

The following case of myeloblastic leukemia illustrates the development of macrocytosis and multilobed neutrophiles, two characteristics of pernicious anemia, by the use of aminopterin.

Case Report

A 54 year old man, admitted to Presbyterial Hospital on September 15, 1948, had been diagnosed 10 months earlier as having chronic myelogenous leukemia. The roentgentherapist had given him 20 roentgen-ray treatments over a period of eight to 10 weeks. When the patient was first studied after this it was found that his red blood cell count was 4,930,000 per cu. mm.; white blood cells, 76,000 per cu. mm.; hemoglobin, 15 gm., and that 28 per cent of the cells were blasts and 18 per cent were

Table I

Date	Day	Microns										Red Blood Cell Count	
		4.5	6.0	6.75	7.5	8.25	9.0	9.75	10.5	11.25	12.0		
9-6-48			1		52	31		14	1	1		4,970,000	
9-23-48			6	2	43	18	25	4	5				
9-24-48	0												Aminopterin in liver started
9-30-48	7 (0)											2,900,000	Aminopterin in saline started
10-3-48	10 (4)				44		52		3	1		3,600,000	
10-7-48	14 (8)		1		41		51		7			3,000,000	
10-13-48	20 (14)											3,900,000	Aminopterin discontinued
10-15-48	21 (16)		5	2	26	16	38	7	4	1	1	3,500,000	
1-17-48	23 (18)	1	3		76		15		5				
10-20-48	26 (21)				59		31	1	7		2	3,080,000	
10-27-48	33 (28)			5	48		43		4			3,790,000	

Red blood cell sizes.

Figures show percentage of each size of red blood cells. The first figure in the column marked "Day" is the number of days after the start of the aminopterin in liver extract. The figure in parentheses is the number of days after the start of aminopterin in saline solution.

"stem" cells. The spleen measured 19.5 cm., the lower border being 9 cm. below the costal margin. The liver measured 20 cm., the lower border being 5 cm. below the costal border.

The patient was treated with Fowler's solution and blood transfusions, without adequate reduction of the leukocyte count. He was then given injections of aminopterin,* 1 mg. daily, dissolved in 1 c.c. (15 units) of liver extract, for eight days. There was no appreciable change in the leukocyte count with this, so the aminopterin was dissolved in saline solution and given daily for two weeks. The leukocyte count decreased from 220,000 per cu. mm. to a minimum of 3,000 per cu.

* Furnished through the kindness of the Lederle Laboratories.

mm. on the seventeenth day. It then increased slowly and rose to 101,200 per cu. mm. the day before death, two weeks later.

The red blood cells showed a tendency to the large forms during the week after aminopterin in saline therapy, decreasing in the following two weeks. There was no general ovalocytosis of the macrocytes, as in pernicious anemia, nor was there an increase in the number of microcytes (table 1). The red blood cell size increase was first noted four days after the aminopterin in saline was started and reached its maximum on the sixteenth day, two days after the aminopterin was discontinued. The red blood cells had not returned to the normal size distribution by the twenty-eighth day, 14 days after the drug was discontinued.

TABLE II

Date	Day	Number of Lobes							Total Leukocyte Count	
		1	2	3	4	5	6	7+		
9–6–48		5	2	6	8	79			76,000	
9–24–48	0									Aminopterin in liver started
9–30–48	7 (0)								220,000	Aminopterin in saline started
10–3–48	10 (4)	1		4	6	89			200,000	
10–7–48	14 (8)	4		8	20	50		18	110,000	
10–13–48	20 (14)								19,000	Aminopterin discontinued
10–15–48	21 (16)			4	5	28	12	51	8,500	
10–17–48	23 (18)				4	30	15	51	5,000	
10–20–48	26 (21)			1	10	38	22	29	4,900	
10–22–48	28 (23)				13	67	11	9	7,600	
10–24–48	30 (25)			13	21	45	15	6	7,000	
10–27–48	33 (28)	10		3	22	48	15	2	80,000	

Figures indicate percentage of neutrophils showing the number of lobes indicated at the head of the column.

A second feature was the development of multilobed polymorphonuclear neutrophils. This began about four days after the start of aminopterin in saline solution and reached its maximum on the eighteenth day. It was still evident two weeks after cessation of the therapy. At the height of the reaction, at least two-thirds of the neutrophils had six lobes or more (table 2).

No improvement in the physical condition, leukocyte count, or change in the red blood cell size or number of the lobes in the neutrophils was noted during the week in which liver extract was given with the aminopterin.

The bone marrow, studied on the seventh day after discontinuing the aminopterin, showed a predominantly normoblastic marrow, with a slight increase in the number of younger forms. "Megaloblasts" (21.0 by 23.5 microns) were present. The ratio

of nucleated red blood cells to leukocytic forms was 1:9. Some very large metamyelocytes were present, measuring 22.5 by 24.0 microns, with kidney-shaped nuclei measuring 13.75 by 21.0 microns. The normal metamyelocytes in this preparation averaged 13.5 by 13.5 microns, with nuclei 13.4 by 9.0 microns.

The red blood cell count on September 6, 1948 was 4,930,000 per cu. mm., white blood cells, 76,000 per cu. mm., and hemoglobin, 15.0 gm. The differential leukocyte count showed mature neutrophils, 25.0 per cent; young neutrophils, 10.0 per cent; metamyelocytes, 7.0 per cent; mature monocytes, 5.0 per cent; young monocytes, 3.0 per cent; metamonoblasts, 1.0 per cent; basophils, 3.0 per cent; blasts, 28.0 per cent; "stem" cells, 18.0 per cent. On September 18, 1948, a gall-bladder roentgen-ray study was made, and on September 20, 1948, the chest and abdomen were studied by fluoroscopy. On September 23, 1948, the leukocyte count was 150,000, and the differential count changed as follows: mature neutrophils, 2.0 per cent; young neutrophils, 3.0 per cent; metamyelocytes, 1.0 per cent; mature monocytes, 2.0 per cent; young monocytes, 2.0 per cent; metamonoblasts, 2.0 per cent; eosinophils, 1.0 per cent; basophils, 1.0 per cent; lymphocytes, 4.0 per cent; blasts, 76.0 per cent; "stem" cells, 6.0 per cent.

Six days after the use of aminopterin in saline solution, the red blood cell count was 3,500,000, the leukocyte count was 48,000, and the differential leukocyte count was: mature neutrophils, 14.0 per cent; young neutrophils, 4.0 per cent; metamyelocytes, 0 per cent; mature monocytes, 2.0 per cent; young monocytes, 2.0 per cent; blasts, 76.0 per cent; "stem" cells, 2.0 per cent.

A week later, four days after aminopterin in saline solution was discontinued, the leukocyte count was 5,000 per cu. mm., and the mature neutrophils were 81.0 per cent; mature monocytes, 4.0 per cent; lymphocytes, 13.0 per cent; blasts, 2.0 per cent. Two days later the patient was exposed to the fluoroscope. The following day the blasts and "stem" cells were 8.0 per cent; two days later, 20.0 per cent, and on the eighth day after exposure, 73.0 per cent with a total leukocyte count of 80,000 per cu. mm.

It is interesting to note that the number of blasts increased within 48 hours of exposing the patient to the roentgen-ray machine, on September 20, 1948, fluoroscopy, and on October 19, 1948, fluoroscopy. The "small" amount of roentgen-ray to which the patient was exposed was apparently enough to initiate the division process in the myeloblasts.

Summary

After the use of aminopterin in a patient in the advanced "blast" stage of chronic myelogenous leukemia, a stage of macrocytosis of the red blood cells and multilobulation of the neutrophils developed. Large metamyelocytes and cells having characteristics of megaloblasts appeared in the bone marrow. These characteristics of the pernicious anemia type of blood and bone marrow picture appeared to be associated with the neutralization of the folic acid effect.

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SYPHILIS OF THE STOMACH *

By PAUL S. FANCHER, F.A.C.P., Colonel, Medical Corps, United States Army

THAT syphilis of the stomach is a comparatively rare lesion is well substantiated by the familiar statistics quoted by Bockus,[1] Stokes [2] and many others. That the diagnosis of the condition is made more frequently than formerly, as asserted by Kauvar and Kauvar,[3] is probably correct. Better diagnostic methods, together with less rigid diagnostic criteria, support this observation. However, their observation that series of cases rather than isolated cases are now reported is not true of the American literature of the last few years. The paucity of American literature since 1940, in contrast to like periods of the past two decades, leads one to contemplate whether the intensified Public Health programs and the more recent methods of treatment and management of early syphilis are not showing some effect.

In 1943, Palmer and his co-workers [4] reported an isolated case of syphilis of the stomach because it was typical and illustrated many of the problems of diagnosis and treatment. Our case is in many ways so analogous to theirs that it is reported in a similar manner.

CASE REPORT

A 35 year old colored truck driver was admitted to the hospital on March 24, 1948, with complaints of fullness and pain in the upper portion of the abdomen, vomiting and weight loss. The abdominal discomfort was first noticed in 1943, but examinations at that time revealed no physical abnormality except a severe pyorrhea. This was treated but no effect was noticed on the symptoms. The patient gradually lost weight but was able to continue to work until two weeks prior to admission, at which time the pain in the upper abdomen became "hard, griping in type." The pain was not referred. He vomited partially digested food streaked with bright red blood one or two times a day. Food aggravated the pain. Weight loss during these two weeks was eight pounds. Stools were normal in color and consistency.

The family history revealed the patient to be the youngest of 23 children. Three brothers and two sisters were living and well, while the remainder had died of unknown causes. The patient's wife had a positive Kahn test but quantitation showed less than 10 Kahn units.

The systemic review was not contributory except that patient had had a chancre in 1942 and a second lesion in 1945. He claimed to have received treatment but, unfortunately, the extent of this treatment was unknown.

Physical Examination on Admission: The general appearance was that of a well developed male who did not appear chronically or acutely ill. Height was 64.5 inches. Weight was 122 pounds, as compared with a normal weight of 138 pounds. The skin and mucous membranes were negative except for multiple small keloids and a penile scar at the site of an old ulcer. Dental hygiene was poor and many teeth were carious. There was moderate enlargement of the inguinal and epitrochlear nodes. The cardiovascular system was normal. The pulse rate was 78 and the blood pressure 104 mm. Hg systolic and 70 mm. diastolic. The respiratory system was normal. The musculoskeletal system was normal. Neurologic examinations were entirely negative. The abdomen was scaphoid and there was tenderness to palpation of the epigastric region. No masses were palpable. The liver, spleen and kidneys were not palpable. Anus and rectum were normal.

* Received for publication May 7, 1949.
From the Medical Service of Percy Jones General Hospital, Battle Creek, Michigan.

Laboratory Examinations: The initial examination of the blood revealed 4.8 million red blood cells, 15.4 gm. hemoglobin, 10,800 white blood cells, with 88 per cent polymorphonuclear cells. The sedimentation rate was 54 mm. in one hour by the Westergren method. Repeated examinations of urine were normal. Examinations of the feces for parasites were negative. The blood serum proteins were reported as 4.4 gm. per 100 c.c. on the initial examination. Two subsequent examinations were reported as 7.4 and 6.4, respectively, with normal albumin-globulin ratios. The blood

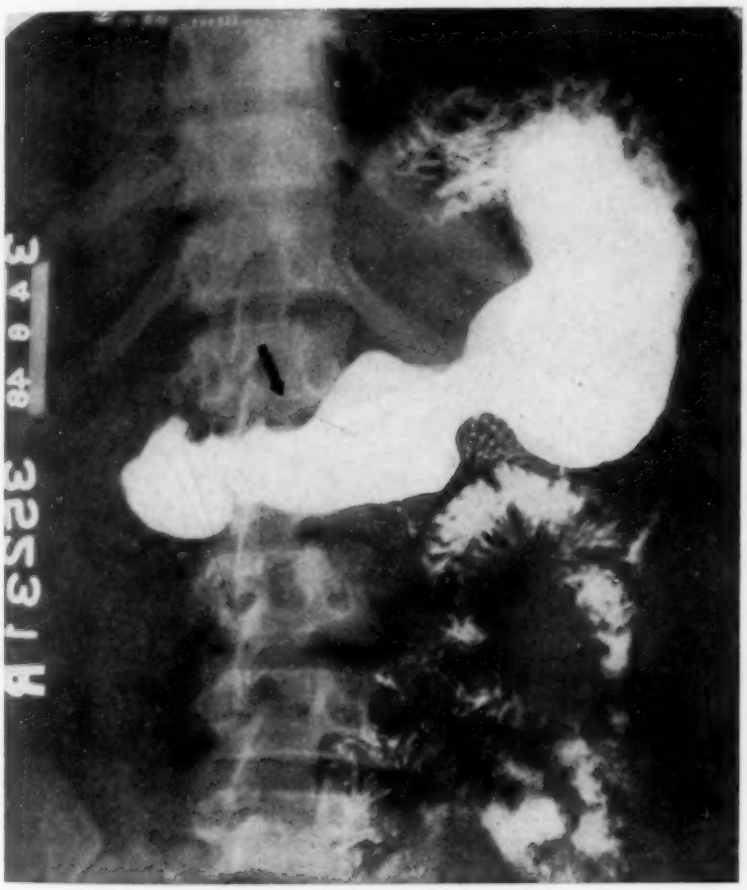

FIG. 1. Demonstrates the persistent filling defect noted on all examinations when the stomach was filled with barium.

cholesterol was 197 mg. per 100 ml., and the esters were 144 mg. per 100 ml. The analysis of the gastric contents revealed an achlorhydria after histamine stimulation. This was not repeated. The Wassermann test was positive and the Kahn test was positive, with a quantitative Kahn of 80 units. After treatment, the Wassermann remained positive but the quantitative Kahn dropped to less than 10 Kahn units. Spinal puncture revealed normal dynamics but, due to the presence of blood, further tests were not made at that time.

Roentgen Examinations: On March 29, the lung fields were clear. The heart was normal in size, shape and position. There were no pathologic findings in the diaphragm, pleura or bony thorax.

On April 5 a gastrointestinal study revealed no evidence of organic disease of the esophagus. A normal mucosal pattern was observed in the upper half of the stomach. However, in the lower half, extending to the pylorus, the walls of the stomach appeared unusually fixed, although not apparently thickened or rigid. There was a loss of the mucosal pattern in the lower half of the stomach. The appearance of the walls suggested a diffuse infiltrating lesion (figure 1). There was marked disturbance at the pylorus, with considerable delay in the passage of barium. At three hours the stomach had retained approximately one-half of the barium and the head of the barium column was in the cecum.

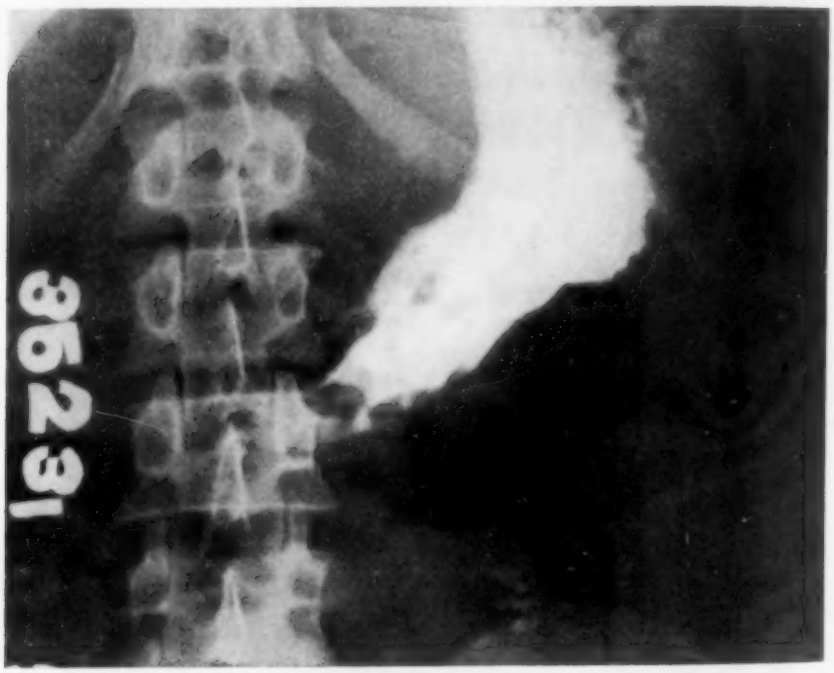

FIG. 2. This special mucosal study demonstrates the disturbed pattern in the distal portion of the stomach. Polyposis was suggested by this examination. Study was made April 9, 1948, after three days of antiluetic therapy.

On April 9, special mucosal studies revealed what was considered to be a polyposis of the lower portion of the stomach (figure 2). The disturbance at the pylorus was again noted, and at no time was the duodenal cap completely filled. The uniformity of the filling defect near the pylorus was considered suggestive of a malignant process.

On May 5, reëxamination again revealed the narrowing and the marked disturbance of the mucosal pattern in the lower one-third of the stomach (figure 3). Peristalsis was not observed in this region during fluoroscopic examination. Irregular collections of barium suggested inflammatory granulation tissue. The walls of the stomach were not definitely rigid. Barium passed through the pylorus with-

out apparent difficulty, even though peristalsis was absent. At five hours the head of the barium column was in the terminal ileum. There was a gastric retention of about one-third of the barium meal. It was thought that, while all the changes could be inflammatory, a low-grade extensive carcinomatous process was more probable.

Gastroscopic Examinations: On April 15, a diffuse, extensive ulcerative lesion was noted involving the antrum and a portion of the angulus. The serpiginous ulceration was shallow with a grayish floor. There was a marginal erythema, but no bleed-

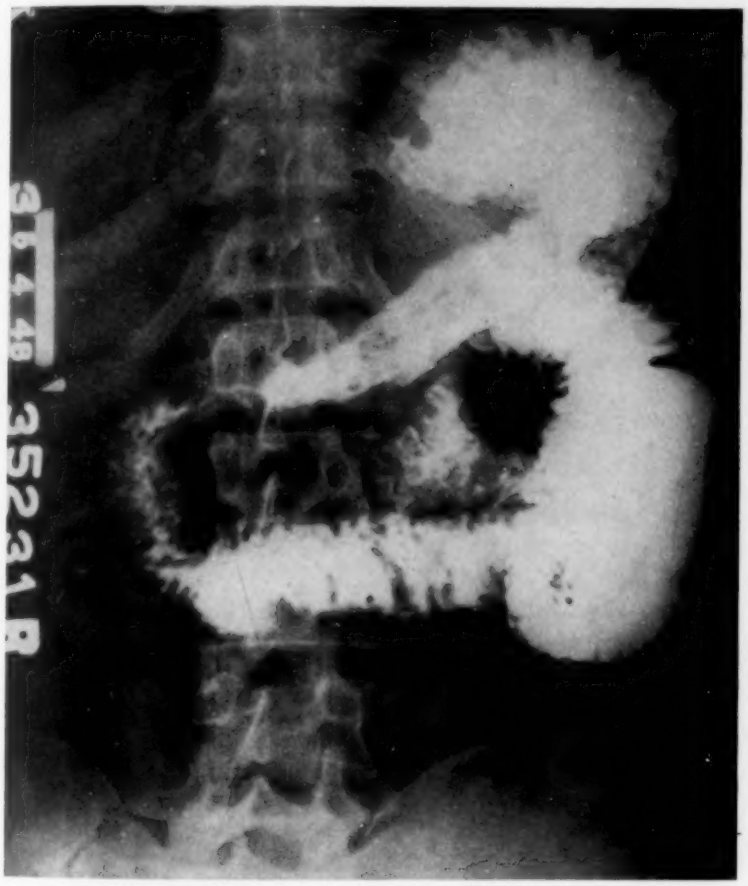

FIG. 3. Demonstrates narrowing of distal portion of stomach and the persistent disturbed mucosal pattern. This study was made after four weeks of intensive antiluetic therapy.

ing was noted. There was obliteration of the rugal pattern, but no localized nodular infiltration was noted. Normal mucous membrane was noted in the fundus of the stomach.

On April 25 the serpiginous-type ulceration appeared somewhat smaller than at the previous examination. Marginal bleeding was noted. A clot of blood was noted in the stomach. Evidence of infiltration was absent. Impression at this examination was of a bleeding prepyloric ulcer with a somewhat malignant appearance.

On May 28 there was little change in the lesion. Considering the roentgen findings, the gastric analysis and the lack of response to antiluetic therapy, it was the impression of the gastroscopist that the lesion was most likely malignant.

Clinical Management and Progress: The management of this case resolved itself into three periods. The treatment was for a peptic ulcer during the initial diagnostic period of 12 days. This treatment consisted of a bland diet, parenteral fluids, antispasmodics and sedatives. During this period the symptoms progressed, as manifested by daily vomiting and continued weight loss.

The second period, of approximately eight weeks, was devoted to intensive antiluetic therapy, based on the knowledge that the patient had an ulcerous lesion of the stomach and a significantly positive serologic test for syphilis. The treatment consisted of 50,000 units of penicillin every three hours for 12 days (total of 4,800,000 units). At the same time, and continuing for the full period, the patient received an

FIG. 4. Gross specimen showing loss of mucosal pattern, ulcerations, edema and thickening of the wall.

initial dose of 40 mg. of mapharsen and subsequent doses of 60 mg. at five-day intervals. In addition, he received 200 mg. of bismuth subsalicylate intramuscularly at weekly intervals. The diet was changed to a modified Meulengracht type, distributed in six small feedings. Clinically the patient improved, in that the vomiting lessened and finally ceased, increasing amounts of food were tolerated, and he gained weight. The quantitative Kahn was less than 10 Kahn units at the termination of treatment.

On May 28, after gastroscopic examination, the case was reviewed and, since malignancy had not been completely ruled out, the patient was referred to surgery. The third period was that of surgical treatment, wherein the patient had a subtotal gastric resection. Aside from a moderate hemorrhage during the first postoperative day, recovery and convalescence were uneventful.

The surgeon reported that the abdominal viscera appeared normal with the

exception of the stomach. The prepyloric area of the stomach was thickened. There was slight scarring on the external surface. No definite mass was palpable.

Pathologic Examinations: Grossly, the material consisted of a portion of the stomach which measured 19 by 12 cm. when opened (figure 4). The serosal surface

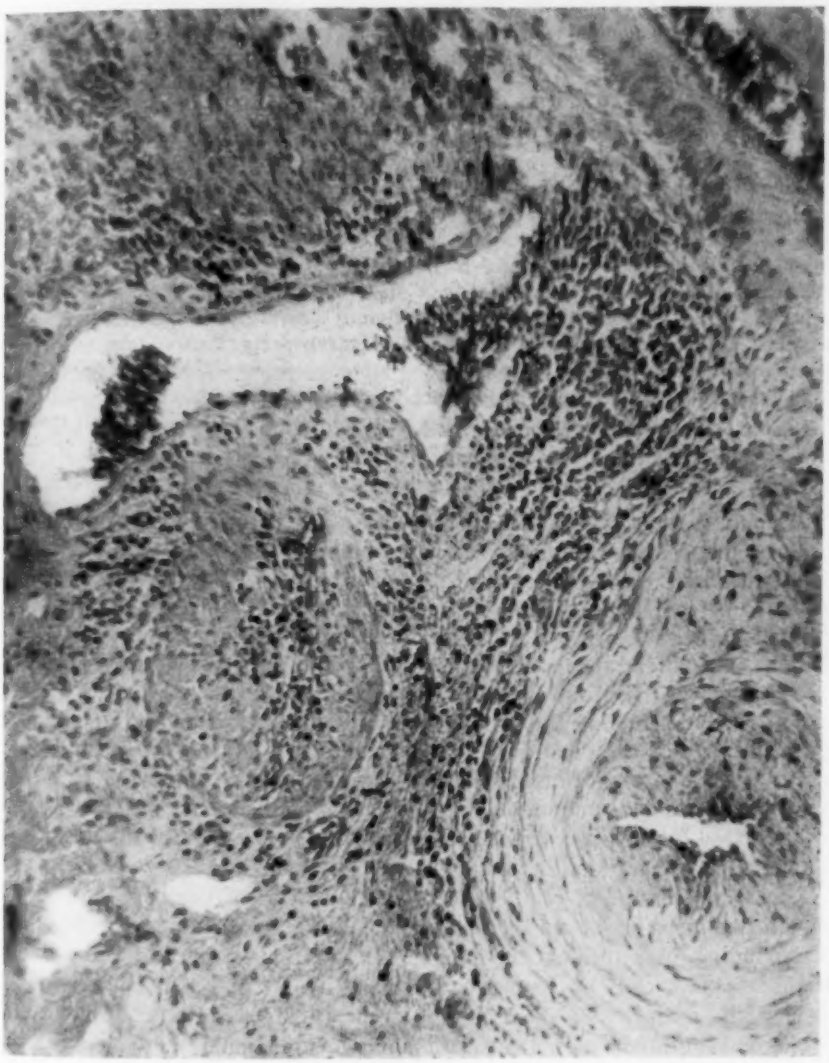

FIG. 5. Demonstrates perivascular cellular infiltration, changes in vascular walls with encroachment on lumen, and increased fibrosis in interstitial tissues.

was smooth. Several shallow ulcers were noted in the mucosa. The largest ulcer, located on the anterior surface of the lesser curvature and 5.5 cm. proximal to the pylorus, measured 3.5 by 2 cm. The ulcer edge was raised and rather sharply demarcated from the surrounding stomach mucosa. The elevated margins were red.

The floor of the ulcer was irregular and brownish-red to gray in color. Several smaller ulcerated areas were noted. The elevated margins measured 1 to 3 mm. in thickness. The pyloric antrum mucosa was thickened and presented a mosaic appearance. Two centimeters of the duodenum were attached to the specimen and were normal in appearance.

Microscopically (figure 5), the largest lesion presented an extensive area in which the mucosa was completely eroded and the muscularis mucosae was obliterated. The base of the ulcer was made up of chronic granulation tissue, which was partly covered by a thin layer of fibrin. The proliferating fibrous tissue contained an infiltrate of lymphocytes, plasma cells and eosinophils. The cells were concentrated about capillaries, arterioles and veins. In many of these vessels they invaded all layers of the wall, while in others they were confined to the adventitia. Some of the larger vessels had an extensive subintimal hyperplasia which almost occluded the lumen. Sections through the antrum revealed an intact mucosa in which cells of the above description infiltrated the tunica propria. In some places distinct follicles were prominent. There was no evidence of malignancy.

It was noted by the pathologist that some of the described changes were suggestive of syphilis. Spirochetes were not found; however, the patient had received intensive antiluetic therapy and the Warthin-Starry preparations were uncontrolled. The comments from the Army Institute of Pathology were: "Most of the staff believe the changes to be consistent with but not diagnostic of syphilis. In most instances the diagnosis of syphilis of the stomach is circumstantial since it is difficult to demonstrate spirochetes."

Discussion

A comparison of the findings in this case with the criteria for diagnosis suggested by many observers indicates that syphilis of the stomach could well have been entertained as the most probable clinical diagnosis. In contrast to the case of early gastric syphilis with associated secondary manifestations reported by Spellberg and Norfleet,[5] wherein the patient appeared "obviously chronically ill," our patient appeared neither acutely nor chronically ill. Probably this case belonged in the group 2 classification of Eusterman,[6] in that the onset was gradual, later resembling the group 1 in that there was pain, vomiting and food aggravation. For the most part, the symptoms in this case fulfilled the clinical diagnostic criteria of Bockus, in that there was untreated tertiary syphilis, there was a demonstrable roentgen defect, gastric symptoms were present which were not alleviated by ordinary management, and there was a clinical improvement following specific antiluetic therapy.

The roentgen studies fulfilled most of the criteria of Carman,[7] and certainly met the two most important of these in that there was a filling defect without a corresponding mass and that the patient was not ill in proportion to the extent of the disease as shown by roentgenogram. Williams and Kimmelstiel [8] pointed out that the majority of these lesions occur in the pylorus and, further, that syphilis is suggested rather than carcinoma when a funnel or tubelike deformity of the distal portion of the stomach is found in a younger individual who is in fairly good clinical condition and who has a positive serologic test. Our findings met these criteria, although the involved portion of the stomach was described as narrowed rather than funnel-shaped. LeWald [9] believed that an experienced roentgenologist could make the diagnosis. This may hold true in a clinic where there is an opportunity to study a series of cases. In isolated cases,

such as that of Palmer and the one we have described, the tendency of the roentgenologist is to describe the findings without interpretation, or to err on the side of safety.

Patterson and his co-workers [10] classified their cases on the basis of the gastroscopic findings. In the ulcerated group the lesions were described as having a smooth, shallow base, sloping edges, and purplish-red, serpiginous borders. Moersch [11] portrayed a somewhat similar picture of the syphilitic ulcer of the stomach. On the other hand, Schindler, in describing the gastroscopic findings in Palmer's case, pointed out that the color manifestations of carcinomatous ulcerations of the stomach are so manifold that they cannot be used as criteria for diagnostic differentiation. The serpiginous nature of the ulceration as found in our case has been described by most observers.

The laboratory findings in our case were not unusual. The positive serology, achlorhydria and failure to demonstrate the *Spirochaeta pallida* have been reported by Bockus, Stokes, Eusterman and others. The pathologic picture was not unlike most reports.

The management of this type of case must be individualized, since the diagnosis is inferential rather than absolute, and since delay in surgery might jeopardize the chance for recovery if the diagnosis is in error. Wessels [12] reported two cases, one of which was operated upon, the other responding satisfactorily to medical treatment. Palmer's patient was operated upon. Knight and Falk [13] reported satisfactory response to medical treatment, yet their case was operated upon for a condition which was considered by them to be an unrelated gastric lesion. Eusterman has claimed that the number of gastrectomies performed in these cases varies with the diagnostic acumen of the physician, yet he advocates the policy of erring on the safe side. Many feel that in cases suspected of gastric syphilis a therapeutic test should be done. However, Williams and Kimmelstiel have pointed out that many gastric lesions will respond somewhat to treatment, and that in many cases it would be unwise to await the response to specific therapy.

Our decision was to give the antiluetic therapy both as a preoperative measure and as a therapeutic test. The type of treatment chosen was penicillin and the older regimen of mapharsen and bismuth. Knight treated his case with penicillin and suggested that the rapid response might have been due to this therapeutic measure. O'Leary [14] favored penicillin because of its more rapid action and fewer complications. He pointed out, however, that final conclusions had not been reached as the period of observation was too short.

Patterson indicated that the gastroscopic examination offered the best means of evaluating the response to the therapeutic test. Our patient improved clinically and serologically. However, after four weeks of treatment there was no demonstrable improvement by roentgen examination. After eight weeks of treatment there was but little improvement demonstrated by gastroscopic examination. Malignancy in our opinion had not been ruled out, therefore surgery was mandatory.

Conclusions

A case of syphilis of the stomach has been presented which typically demonstrated the problems of differential diagnosis and management.

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13. Knight, W. A., and Falk, A.: Tertiary gastric syphilis, Gastroenterology **9**: 17–27, 1947.
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EDITORIAL

THE COMMON COLD AND THE ANTIHISTAMINES

FOUR hundred million common colds, causing a work loss of one hundred million days, are estimated to occur each year in the United States. This is said to represent a wage loss of approximately two billion dollars. The common cold is therefore a problem of great importance from the points of view of both morbidity and economics—not to mention personal inconvenience and discomfort.

As there are few individuals who enjoy immunity to this disease, the "cold cure" is naturally a subject of catholic appeal and therefore a fruitful field for advertising. Supposed cures in the past have monotonously come and gone, but the vogue of antihistaminic therapy continues to enjoy commercial success. It appears that about $100,000,000 were invested in these "cures" by the people of America in 1950.

The first hint that the antihistaminics might be of value in the common cold came from Brewster [1] in 1947. He used benadryl in "well over 100 cases" and believed that it completely aborted the colds in about 10 per cent, and greatly curtailed the remainder. In his next report [2] he had treated 572 patients with five antihistaminics—benadryl, pyribenzamine, thenylene, neoantergan, histadyl—and this time had run a small control series of 77 patients given a mixture of papaverine and codeine. He could distinguish no difference in the efficacy of the five antihistaminics, but he felt that the earlier medication was begun the more effective it proved to be. Thus he claimed that 19 of 21 patients, treated within the first hour of onset of symptoms, were cured. This small group furnishes the basis of the oft repeated claim that the antihistaminics will cure "90 per cent" of patients treated early. It is unnecessary to emphasize how fallacious the *early* diagnosis of a cold can be.

He also claimed a cure rate of 48 out of 55 (87 per cent) treated within the first two hours, 116 out of 156 (74 per cent) treated within the first six hours, and 165 out of 234 (70 per cent) treated within the first 12 hours after onset. Among the control patients only seven out of 22 treated within the first 12 hours were cured. Brewster concludes that abortion of the disease is possible in 90 per cent of patients receiving treatment within the first few hours; "failing this their continued use as palliative treatment shortens the period of morbidity and eliminates many complications. . . . If properly and universally used, the antihistaminics could reduce the incidence of colds to near the vanishing point."

[1] Brewster, J. M.: Benadryl as a therapeutic agent in the treatment of the common cold, U. S. Nav. Med. Bull. **47**: 810, 1947.

[2] Brewster, J. M.: Antihistaminic drugs in the therapy of the common cold, U. S. Nav. Med. Bull. **49**: 1, 1949.

Meanwhile Gordon [3] and Murray [4] had each reported a series of successes. Gordon's report dealt with the treatment of over 500 patients with three antihistaminics—benadryl, pyribenzamine, thephorin—and his impression was that 8 per cent of colds were completely aborted, while a total average of 85 per cent "experienced a more comfortable and shorter convalescence than anticipated by doctor or patient." Murray presented results in 494 patients treated with pyribenzamine. He claimed that 110 lost their symptoms in 24 hours or less; 204 lost or almost lost their complaints in two or three days; while 83 were "greatly improved" but had colds which lasted six to seven days. In 97 there was no improvement. Thus 75 per cent were cured or had their symptoms alleviated. Murray concluded that the drug seemed to produce more cures and more relief from annoying symptoms than any other treatment used in his medical department for 28 years.

It is worth noting that Diehl [5] in 1933 had carried out studies on the common cold at the University of Minnesota. He treated large numbers of students with various mixtures of opiates and obtained "definite improvement" in 74 to 78 per cent of patients with acute coryza. He gave lactose placebos to a control series, and obtained good results in 35 per cent of these also. He comments that this success with placebos is "indicative of the spontaneous improvement in acute colds for which any medication that happens to be taken is given credit. It is because this percentage is so large that it is possible to convince the public that practically any preparation is of value for the prevention or treatment of colds. In fact, some of the comments that were made on the report cards by persons who had received only lactose tablets would serve admirably as testimonials concerning the value of these tablets for the treatment of colds."

In the present antihistaminic era, the first word of caution on this subject came from Paton, Fulton and Andrewes [6] in a letter to the editor of the *Lancet*. Dissatisfied with the enthusiastic reports they had read, they warned, "potential cold cures should be subjected to most rigorous tests; these must include provision of approximately equal groups of patients receiving test drug and placebo, and exclusion of all possibility that either patient *or clinical observer* has any suspicion as to who belongs in which group."

Acting on these principles these authors carried out a brief trial on small numbers—10 patients on neoantergan and 10 on lactose placebos. Results were summarized as follows:

[3] Gordon, J. S.: Antihistaminic drugs in the treatment of upper respiratory tract infection, Laryngoscope **58**: 1265, 1948.
[4] Murray, H. G.: The treatment of head colds with an antihistaminic drug, Indust. Med. **18**: 215, 1949.
[5] Diehl, H. S.: Medicinal treatment of the common cold, J. A. M. A. **101**: 2042, 1933.
[6] Paton, W. D. M., Fulton, F., and Andrewes, C. H.: Letter to Editor, Assessment of "cold cures," Lancet **1**: 935, 1949.

"Patients' opinions—Of the 10 who received the placebo, 4 benefited, 4 did not, 2 could not say. Of the 12 receiving neoantergan, 4 benefited, 7 did not, 1 could not say.

Average duration of the cold—In those receiving the placebo, this was 6.2 days; in those receiving neoantergan, 6.5 days.

Examiner's estimate—On the working assumption that the drug was beneficial, the examiner attempted, after weighing all the available facts, to place correctly each of 17 patients into either the 'drug' or 'placebo' group. Of the first 8 cases, his estimate was correct in 7; but, alas, in the succeeding 9 he was wrong 8 times."

This small, numerically inadequate series, was at least an experiment scientifically conceived and executed. It throws into naked relief the pattern of the antihistamine trials thitherto conducted. Brewster's, Gordon's and Murray's series lacked adequate controls, they relied solely on subjective evaluation for diagnosis and effect of treatment, there were no rigid standards laid down for evaluating the effects of the different drugs employed, there was no satisfactory statistical analysis of their results, and both doctor and patient knew what each patient was receiving.

Yet it was on the strength of these experiments alone that the drug-makers pushed for and the Food and Drug Administration granted permission for free and easy sale of the antihistaminics as cold cures.

Brewster's [7] third publication records his results in 1,019 patients treated with thephorin. For this series he used 195 controls. From these later results it was already apparent that Brewster's percentages of cures were already deteriorating. Thus he claimed "cures" in only 54, instead of 74, per cent of his six hour group, and in only 46, instead of 70, per cent of his twelve hour group. Significantly enough he also reported 32 per cent cures in his six hour group on placebo medication. His later results are therefore clearly not so dramatic as his earlier findings.

Arminio and Sweet [8] appear to introduce objective evaluation for the first time. They examined 311 patients suffering from colds, and according to their findings divided the affliction into three stages. They gave neohetramine to 104 patients, and found that all 86 who received the drug within 48 hours of the onset of symptoms responded to the treatment. Another group of 106 were given a placebo and the duration of the disease did not appear to be affected. The remaining 101 patients received the usual symptomatic treatment for colds (nose drops, etc.), and these also derived no benefit.

They also ran a prophylactic study. One hundred patients received 50 mg. of the drug once daily, another 100 received it twice daily, and an-

[7] Brewster, J. M.: Treatment of common colds with an antihistaminic drug, Illinois M. J. **96**: 302, 1949.

[8] Arminio, J. J., and Sweet, C. C.: The prophylaxis and treatment of the common cold with neohetramine (thonzylamine hydrochloride), Indust. Med. **18**: 509, 1949.

other 100 three times daily. Three hundred further patients received placebos. Nearly 90 per cent of the three groups receiving the drug in varying dosage failed to contract a cold, while 241 out of the 300 on placebos developed colds (80 per cent).

These results are undoubtedly statistically significant; yet the experiment is vitiated by the fact that it was known to the clinical observers which patients were receiving neohetramine and which were receiving the placebo. All careful investigators know well that the doctor's enthusiasm for a drug may be communicated to his patient with remarkable effect on symptoms; and moreover, despite the best and most honest intentions, such enthusiasm can distort an investigator's objectivity in estimating the results of treatment.

Phillips and Fishbein [9, 10] used a compound containing chlorothen citrate, phenacetin and caffeine (caubren compound) in the treatment of 135 patients, with a control series of 120 receiving aspirin. All receiving the compounds derived some benefit. A quarter of those receiving the drug within 24 hours of onset lost all their symptoms within a day, while a total of 69 per cent of those receiving it early lost their symptoms within three days. On aspirin 52 per cent of 91 patients reported relief within three days, 15 per cent within one day. The average duration of colds in those taking the compound was 2.3 days, as contrasted with six days on aspirin.

Tebrock [11] then reported the largest series to date on 1,745 industrial employees. Of these 782 received neohetramine prophylactically, while 250 controls received placebos. In the neohetramine group colds were observed in 22.8 per cent, while they occurred in 65 per cent of the control series. In actual treatment of the disease 963 received the drug, in whom "effective therapeutic results" were claimed in 83 per cent. Tebrock concludes "the antihistamines are not a cure for the common cold. . . . Their effect is entirely symptomatic. However, by aiding and keeping the upper respiratory mucosa in a state of normal physiological function, the natural defense mechanisms against bacterial and viral invasion are sustained." This conclusion is clearly open to serious question. It has been pointed out that the secretion which characterizes the onset of a head cold is presumably a natural defensive mechanism whereby the body attempts to dilute and wash away the noxious stimulus. To dry up such secretion with atropine, ephedrine or the antihistamines is probably to interfere with a natural and beneficial process.

Kessler [12] treated 1,000 industrial workers with hydryllin. Of these 83.7 per cent reported slight to marked improvement. Of 100 controls,

[9] Phillips, W. F. P., and Fishbein, W. I.: An antihistaminic analgesic preparation in the therapy of colds—a preliminary report, Indust. Med. **18**: 526, 1949.

[10] Phillips, W. F. P., and Fishbein, W. I.: An antihistaminic analgesic preparation in the therapy of colds—final report, Indust. Med. **19**: 201, 1950.

[11] Tebrock, H. E.: Management of the common cold with neohetramine (Anahist)—a preliminary report, Indust. Med. **19**: 39, 1950.

[12] Kessler, M. M.: Hydryllin for the common cold, J. M. Soc. N. J. **47**: 29, 1950.

on the other hand, 93 per cent were unimproved. Kessler claimed that man hours lost through colds were reduced by nearly two thirds following the introduction of this program.

In February 1950 the Council on Pharmacy and Chemistry of the American Medical Association [13] published a report on the antihistamine situation. They drew attention to the numerous flaws in the statistical results published up to that time. They emphasized that diagnostic methods had not conclusively demonstrated that all the conditions treated were actually common colds. While accepting the prophylactic study of Arminio and Sweet as suggestive and statistically significant, they pointed out that it still required to be verified by other workers because of the small numbers involved and because of the fact that their results ran contrary to the expressed opinions and experience of many allergists.

The Council concluded that further experiments were essential, and recommended that tests be carried out on volunteers inoculated with cold virus. "Until a scientifically acceptable study is performed, the true effectiveness of the antihistaminic drugs in the control of the common cold cannot be evaluated."

At about this time the tide turned. Hitherto, with the single exception of the small but important communication of Paton and his colleagues, there had been none but encouraging reports of the efficacy of these drugs in the treatment of the common cold. From that time on, however, there has been a steady, almost uninterrupted ebb of the euphoric tide.

The first discouraging report came from Feller [14] and his coworkers at Western Reserve University. Space does not permit a detailed outline of this investigation, nor of the flood of convincing negative results which have followed it. The workers at Western Reserve concluded that none of the antihistaminics used had any influence on the duration of satisfactorily diagnosed colds, nor was any prophylactic potency demonstrated in a small series of inoculated volunteers.

In Shaw and Wightman's [15] study at Cornell involving over 200 students in both the treated and placebo groups, 53 per cent of the treated group believed they had been helped, while 50 per cent of the placebo group thought likewise.

Hoagland and his colleagues,[16] Cowan and Diehl,[17] a committee ap-

[13] Report of the Council on Pharmacy and Chemistry on antihistaminic agents in the prophylaxis and treatment of the common "cold," J. A. M. A. **142**: 566, 1950.

[14] Feller, A. E., Badger, G. F., Hodges, R. G., Jordon, W. S., Rammelkamp, C. H., and Dingle, J. H.: The failure of antihistaminic drugs to prevent or cure the common cold and undifferentiated respiratory diseases, New England J. Med. **242**: 737, 1950.

[15] Shaw, C. R., and Wightman, H. B.: A study on the treatment of the common cold with an antihistaminic drug, New York State J. Med. **50**: 1109, 1950.

[16] Hoagland, R. J., Deitz, E. N., Myers, P. W., and Cosand, H. C.: Antihistaminic drugs for colds: evaluation based on a controlled study, J. A. M. A. **143**: 157, 1950.

[17] Cowan, D. S., and Diehl, H. S.: Antihistaminic agents and ascorbic acid in the early treatment of the common cold, J. A. M. A. **143**: 421, 1950.

pointed by the Medical Research Council of Great Britain,[18] Lorriman and Martin,[19] personnel of the U. S. Naval Medical Research Unit No. 4 at Great Lakes,[21] Browning,[23] and Lowell and his coworkers,[24] have all subsequently reported well controlled studies, and from none of these has any evidence emerged that the antihistamines are of value in treating the common cold. These seven investigations involved a total of over 5,000 persons. Fabricant [22] has also recently stated that in controlled studies at the University of Illinois College of Medicine and the Chicago College of Optometry there was no indication that any of the used antihistamine drugs prevented, aborted or shortened the common cold.

At least three less discouraging reports, however, have recently appeared. In a huge series involving 8,538 cases Manson et alii [27] reported that coricidin (a compound produced by Schering Corporation containing chlortrimeton, aspirin, phenacetin and caffeine) relieved symptoms in 72.7 per cent of 5,734 treated patients, as against 59.3 per cent of 1,539 treated with A.P.C., and 54.2 per cent of 1,265 given placebos. Estimates of relief appear to have been based solely on "yes" or "no" answers to the question "did medication relieve symptoms?" submitted on data cards. In a study by Hirsh,[28] which appears to have been well controlled and involved 1,008 patients, there was evidence that the symptoms of colds were better controlled by trimeton than by lactose placebos; the author concludes "the antihistaminic . . . does not completely cure the 'common cold,' but does alleviate some of the symptoms and, in some instances, shortens the course of the disease by varying degrees." There was some evidence that purulent complications were less frequent (2 per cent) in the trimeton treated group than in the controls (5 per cent).

[18] Report by a Special Committee of the Medical Research Council: Clinical trials of antihistaminic drugs in the prevention and treatment of the common cold, Brit. M. J. 2: 425, 1950.

[19] Lorriman, G., and Martin, W. J.: Trial of Antistin in the common cold, Brit. M. J. 2: 430, 1950.

[20] Baughn, W. L.: Antihistamine chemicals in the treatment of the common cold—report on a twenty-seven month study, Indust. Med. 19: 413, 1950.

[21] Personnel of U. S. Naval Medical Research Unit No. 4, The prophylaxis and treatment of acute respiratory diseases with antihistaminic drugs. I. Prophylactic treatment in Navy male recruits, J. Lab. and Clin. Med. 36: 555, 1950. II. Prophylactic treatment with therapeutic dosage in Navy male recruits, *ibid.* 36: 570, 1950. III. Treatment of minor acute respiratory infection in Navy WAVE recruits, *ibid.* 36: 576, 1950. IV. The prophylaxis and treatment of "colds" in volunteers, *ibid.* 36: 584, 1950.

[22] Fabricant, H. D.: Antihistaminic drugs and the common cold: a critical review, Am. J. M. Sc. 220: 464, 1950.

[23] Browning, R. H.: The early treatment of common colds with an antihistamine—Histadyl, New England J. Med. 243: 994, 1950.

[24] Lowell, F. C., Schiller, I. W., Alman, J. E., and Mountain, C. F.: The antihistaminic drugs in the treatment of the common cold, New England J. Med. 244: 132, 1951.

[25] Wyngaarden, J. B., and Seevers, M. H.: The toxic effects of antihistaminic drugs, J. A. M. A. 145: 277, 1951.

[26] Editorial, Antihistaminic drugs and the common cold, Brit. M. J. 2: 448, 1950.

[27] Manson, M. H., Wells, R. L., Whitney, L. H., and Babcock, G.: Coricidin in the treatment of the common cold, Internat. Arch. Allergy App. Immun. 1: 265, 1951.

[28] Hirsh, H. L.: A controlled study of the treatment of upper respiratory infection with prophenpyridamine (Trimeton), Am. Pract. 2: 32, 1951.

Baughn [20] records his results in a large group of industrial employees—a total of 4,627 treated with 1,336 controls. Several antihistaminic drugs were employed and the controls received an A.P.C. compound. Apparently 66 per cent of the treated patients had complete clearing of symptoms in 48 hours, while only 27 per cent of the controls made this claim. On examining the contemporaneous rate of absenteeism, however, and the ratio of colds experienced to colds expected, Baughn failed to observe any reduction in either, as would be expected if the drugs were of value. There is no statement in this report to the effect that either subjects or doctors were unaware of the type of medication used in each case, and in default of this it must be assumed that no attempt was made to conceal the nature of the medications.

All in all it seems fair to say that since carefully controlled studies have largely replaced the observations of "impressionists," overwhelming evidence is accumulating that, much as it is to be regretted, the antihistamines are not the answer to our prayers for a cold cure.

Apart from their ineffectiveness, they are not as innocuous as they have been advertised to be. Side reactions from them may at times have been overemphasized. Some observers have recorded almost as high an incidence of claimed side-reactions from an inert placebo as from one of the antihistaminics.[15, 18] There can, however, be no doubt that at times these drugs produce incapacitating and even dangerous toxic effects. This whole subject has lately been reviewed by Wyngaarden and Seevers.[25]

These authors list over 60 symptoms and signs of acute toxicity which have been reported in humans. Reactions have involved the nervous, gastrointestinal, cardiovascular, respiratory, genitourinary, and hematological systems, as well as the skin and mucous membranes. The most important effects, however, are the central depressant effect in adults, the convulsive susceptibility of children, and effects on the blood.

The central depressant effect is of course of paramount importance in those engaged in operating dangerous machinery, in automobile drivers, and in airplane pilots. Eight deaths in children under two years have been reported, with convulsions as the cause of death in most of these. Accidental deaths in children from this cause are particularly tragic when it is considered that the drug is useless for the purpose for which it has been purchased and placed upon the bathroom shelf. Apart from fatalities in infants resulting from accidental overdosage, there have been a number of such accidents both in children and adults with serious consequences but with eventual recovery.

Of the three fatal cases so far reported in adults, one occurred from agranulocytosis, one from central nervous system depression (suicide with 1,500 mg. of benadryl), and the third followed the ingestion of only 200 mg. of benadryl in a severe asthmatic; this last death cannot unequivocally be attributed to this drug alone.

Besides the fatal case of agranulocytosis, eight other nonfatal cases have been reported as well as three of nonfatal hemolytic anemia. There is good evidence that these drugs should be used with special caution in epileptics and in patients suffering from heart disease. Thus there are a number of reasons—apart from their inefficacy—for pausing before prescribing the "harmless" antihistaminics for the common cold.

At best the task of assessing a cold cure is beset with difficulties. Diagnosis is often uncertain in the early stages—unmistakable symptoms will not infrequently vanish into thin air; once established the course of the common cold is notoriously variable; and as patients and doctors appear to be particularly suggestible, it is hard to eliminate bias from the investigation. As has been pointed out, a high percentage seem to be cured by the very thought of a new remedy. It is therefore of first importance that studies to evaluate such "cures" should be highly integrated and most carefully controlled, with all possible steps taken to escape bias. In the absence of such an approach investigations will be meaningless.

H. J. L. M.

REVIEWS

Hormones and Behavior: A Survey of Interrelationships between Endocrine Secretions and Patterns of Overt Response. By FRANK A. BEACH. 368 pages; 16 × 24 cm. Paul B. Hoeber, Inc., Medical Book Dept. of Harper and Bros., New York. 1st ed. 1948. Price, $6.50.

This book assembles in one volume our knowledge about the behavior of animals and man, as influenced by the presence or absence of the hormones. More is said about animals than man, but this fact in no way detracts from the interest or the usefulness of the book. The possibility that hormones may influence behavior has occurred to many people and the literature on this subject is plentiful but scattered. Here for the first time it is drawn together into one book. Dr. Beach is well qualified for the task since, as Professor of Psychology at Yale University, he has contributed greatly to the pioneer work in this field.

For the most part the book is a review of the published literature, occasionally enlivened by the author's illuminating comment. It will be invaluable to the student, and will serve as an excellent orientation in this difficult and complex subject.

Among the behavior patterns which receive the heaviest treatment are those related to sexual activity (including mating, courtship, parturition, and parental care), social behavior (including aggression, submission, conditioning and learning), and the patterns associated with the migratory and locomotor habits of animals. The bibliography contains over 600 titles and thoroughly covers the literature in this field. Its newness is attested to by the fact that, with rare exceptions, most of the titles appeared after 1930.

The author has an excellent grasp of the validity of the methods used in this field and his evaluation of them is well worth reading for its own sake. These investigations usually proceed along the lines of determining the effect of varying amounts of a single hormone upon some easily recognizable manifestation of a complex behavior pattern. The author properly emphasizes the artificiality of such situations. He also points out that the behavior patterns most affected by hormones are those which fall within the category of instinctive responses, a conclusion which seems amply justified by the evidence. Therefore, the basic primitive functions are more subject to humoral control than are the recently acquired, learned responses. Conversely, the more entirely behavior is under nervous control, the less modifiable it is by hormones. This conception leads to interesting connotations (not stressed by the author) on the modification of basic behavior by the nervous system in man. How far sexual behavior in the higher forms is a matter of endocrine control and how far it is a learned response are still matters for conjecture.

It comes as no surprise to find that many of the primitive responses are altered by social conditioning. To what extent these alterations are related to the prevalence of psychogenic disorders among our species is hard to determine, but any student of psychosomatic medicine would do well to become familiar with the primitive behavior patterns described in this book. The practicing physician will find much here to give him thought, although little to put to immediate use.

Close study and analysis show similarities between human behavior and animal behavior in certain basic situations. Social dominance, or "peck order" apppears in vertebrates as lowly as the fish. This behavior is modified in striking ways by hormones, particularly by the estrogens and androgens. No one knows what determines peck order in the human, but the forces which operate in other mammals must have some effect in man as well. Man experiences the release of adrenaline in times

of emotional stress, but the responses usually seen in animals are suppressed and hidden in the human. However, the effects on the circulatory and digestive system in man have long been appreciated by physiologists.

Questions such as those discussed above arise naturally after reading this book. Its value undoubtedly lies in the creation of an awareness of new fields of exploration, always a refreshing experience for any reader.

DIETRICH C. SMITH

Electroencephalography in Clinical Practice. By ROBERT S. SCHWAB, M.D., Director of the Brain Wave Laboratory, Massachusetts General Hospital, and Associate in Neurology, Harvard Medical School. 195 pages; 16.5 × 25.5 cm. W. B. Saunders Company, Philadelphia. 1951. Price, $6.50.

This monograph is a useful addition to the small but growing list of texts on electroencephalography. "Primarily intended for neurologists, internists, psychiatrists, and neurosurgeons," the author states that it is not a manual for the electroencephalographer. Within these limits, however, the purpose of the book "to discuss the uses and limitations of electroencephalography in the diagnosis and study of diseases of the nervous system" is well achieved. A very happy selection of illustrations and case examples coupled with clear diagrams makes the text a pleasure to read.

The discussion of neurophysiology is brief but the emphasis on electrical field spread is a timely concept in understanding the rhythmic spontaneous activity of the brain neurons. In his brief chapter on research, the author points out the value of the EEG to the neurophysiologist and clinical investigator.

Space has been saved in the section on the abnormal electroencephalogram by a summary tabulation of the degree of abnormality in relation to frequency, amplitude, and occurrence of the different wave forms.

The larger chapters have appropriately been devoted to technic, the EEG in epilepsy, and neurological and neurosurgical problems. In these sections, the author has utilized his great experience, both in clinical and research applications, in a clear exposition of modern methods and criteria necessary to obtaining and evaluating the EEG under different conditions. Particularly valuable is the discussion of special technics used in activation of abnormal activity, including the metrazol and stroboscope flash methods. Also useful is the brief listing of the different types of minor and major seizure characteristics in relation to abnormal brain-wave patterns and the value of the EEG in differential diagnosis.

The great importance of this technic in neurological and neurosurgical problems is demonstrated by the long and interesting chapter devoted to trauma, vascular lesions, brain tumor and the surgical treatment of epilepsy. In psychiatric problems, less material is available but the use of the EEG in differential diagnosis and in relation to pre and post shock examination is discussed.

Especially valuable to those beginning the use of this technic is the excellent treatment of laboratory organization, training of staff, and interpretation of records.

The book as a whole is very well written and has the great virtues of clarity and conciseness.

ROBERT H. OSTER

Pain and Its Problems. Edited by SIR HENEAGE OGILVIE, K.B.E., D.M., M.Ch., F.R.C.S., and WILLIAM A. R. THOMSON, M.D. 194 pages; 14.5 × 22 cm. The Blakiston Company, Philadelphia and Toronto. 1951. Price, $3.00.

This is a valuable aid to the clinical study of the most commonly encountered symptom, pain. It is the latest addition to the "Practitioner Handbook" series, and as such many of the chapters have already appeared in that excellent monthly publica-

tion *The Practitioner;* on the other hand several new sections have been written expressly to complete the scope of this text. Each chapter is written by a leading British authority, and the contents are designed to aid in elucidating the three main problems posed by every pain—the course of its conveying fibers, its significance in diagnosis and its relief.

The two introductory chapters are written by internationally recognized authorities on their subjects. The first is on the physiology of pain by Professor Adrian, and the second deals with some clinical aspects of pain and is contributed by Gordon Holmes. In this second chapter it is disappointing to find a rather incomplete schema suggested as a guide for the interrogation of a patient suffering from pain.

The threads of the fundamental themes embodied in the first two chapters are gathered together in the next by Lord Moran under the heading The Meaning and Measurement of Pain. The ensuing 12 chapters are devoted to the problems of pain in various regions or systems—Cardiac Pain, Pain in Peripheral Vascular Disease, Pain in Respiratory Disease, Pain in Disease of the Nervous System, Headache, Pain in the Gastro-Intestinal Tract, Abdominal Pain, Urological Pain, Pain in Gynaecology, Analgesia in Labour, Pain in Rheumatic Diseases, and Dental Pain. All of these chapters are useful, though perhaps those dealing with abdominal and urological pains are particularly so.

The concluding three chapters deal with general subjects. Pain of Non-Organic Origin is a brief and excellent survey of a vast field and should help to orient the practitioner's mind to the psyche of his complaining patient. Although treatment is briefly touched upon at the end of each chapter, the final two renew the subject in a more general way. The first gives a resumé of the important principles that the therapist should keep before him when dealing with pain, and the final chapter deals with a specialized but important aspect of the subject, the relief of pain in childhood.

This arrangement of the text, which is extremely readable, involves a certain amount of overlap and repetition which does not detract from its worth. At times one is disappointed by the omission of helpful points or the unnecessarily sketchy treatment of a subject—but perhaps one is inclined to expect too much in the execution of an idea which is so well conceived. It is undoubtedly true to say that every student and most doctors would benefit from reading and digesting the simple contents of this modest volume. Any text which approaches medicine via symptoms and does the job well deserves high commendation.

H. J. L. M.

Heart Disease, Its Diagnosis and Treatment. By EMANUEL GOLDBERGER, B.S., M.D., Associate Attending Physician, Montefiore Hospital, New York. 651 pages; 15.5 × 24 cm. Lea & Febiger, Philadelphia. 1951. Price, $10.00.

This new book on heart disease is not encyclopedic, nor is it a concise summary of our present knowledge of this important subject. When compared with the recognized authoritative texts in this field, this volume does not seem to be as well organized, as complete, as easily read or as sound. It presents no significant advantages over most of the existing volumes on cardiology.

S. S.

Urgent Diagnosis without Laboratory Aid: A Discussion of the External Signs of Conditions Which Threaten Life. By PROF. DR. HANNS L. BAUR, a.o. Professor of Internal Medicine, University of Munich. 89 pages. 14.5 × 23 cm. Charles C Thomas, Springfield, Illinois. 1950. Price, $2.00.

This little monograph has a worthy purpose. "Many physicians and teachers and consequently many medical students pay too little attention to the signs of disease

that may be garnered at the bedside by one who is willing to train his senses and keep them sharpened by earnestly attempting to arrive at a diagnosis without laboratory aid. The strongest tendency today is to lean too heavily on x-ray and clinical laboratory techniques and to neglect the use of the senses." The purpose of this text is to marshall for the physician facing an emergency those features which his "eyes, ears, nose and touch" can appreciate.

Dr. Baur deals in turn with nervous manifestations; facies, position and attitude; abnormal odors; cutaneous manifestations; disorders of respiration; urinary symptoms; and gastrointestinal manifestations.

On the whole the text is disappointing. It is not adorned with the clinical observations that one, perhaps unjustifiably, expects. The worst fault, however, seems to lie with the translators, who have not done their author justice. The meaning is far from clear in many places, and the text's construction leaves much to be desired in others. What can "a tendency to a strange change in the pulse" mean? And what could be more clumsily phrased than "the constipation as to flatus is the more reliable sign than as to stools"?

Altogether there appears to be no adequate reason for recommending perusal of this brief text, except that it serves to emphasize the worthy principles of bedside observation. It is much to be regretted that a book devoted to such a high purpose cannot be accorded higher praise.

H. J. L. M.

BOOKS RECEIVED

Books received during May are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

The American Illustrated Medical Dictionary: A Complete Dictionary of the Terms Used in Medicine, Surgery, Dentistry, Pharmacy, Chemistry, Nursing, Veterinary Science, Biology and Medical Biography with Their Pronunciation, Derivation and Definition. 22nd Ed. W. A. NEWMAN DORLAND, A.M., M.D. F.A.C.S., Lieutenant-Colonel, M.R.C., U. S. Army, former member of the Committee on Nomenclature and Classification of Diseases of the American Medical Association. 1736 pages; 25 × 16.5 cm. 1951. W. B. Saunders Company, Philadelphia. Price, $10.00.

Biological Actions of the Adenine Nucleotides. By H. N. GREEN, M.A., M.D., M.Sc., Professor of Pathology, University of Sheffield, and H. B. STONER, M.D., B.Sc., Research Assistant, Department of Pathology, University of Sheffield; with a Foreword by SIR EDWARD MELLANBY, G.B.E., K.C.B., F.R.S., M.D., Sc.D., F.R.C.P. 221 pages; 22 × 14.5 cm. 1950. H. K. Lewis & Co., Ltd., London. Price, 25s. net.

Clinical Electrocardiography. By ASHTON GRAYBIEL, Captain, MC, USN, Director of Research, U. S. Naval School of Aviation Medicine, Pensacola, Florida. 198 pages; 25.5 × 18 cm. 1950, 1951. Thomas Nelson & Sons, New York. Price, $5.00.

Conference on Problems of Aging: Transactions of the Twelfth Conference, February 6–7, 1950, New York, N. Y. Edited by NATHAN W. SHOCK, Chief, Section of Gerontology, National Heart Institute, National Institutes of Health and The Baltimore City Hospitals, Baltimore, Md. 215 pages; 23.5 × 15.5 cm. 1951. Sponsored and published by the Josiah Macy, Jr. Foundation, New York. Price, $3.50.

Connective Tissues: Transactions of the First Conference, April 24–25, 1950, New York, N. Y. Edited by CHARLES RAGAN, Department of Medicine, College of Physicians and Surgeons, Columbia University. 164 pages; 23.5 × 15.5 cm. 1951. Josiah Macy, Jr. Foundation, New York. Price, $3.25.

Cybernetics: Circular Causal and Feedback Mechanisms in Biological and Social Systems: Transactions of the Seventh Conference, March 23–24, 1950, New York, N. Y. Edited by HEINZ VON FOERSTER, Department of Electrical Engineering, University of Illinois; Assistant Editors: MARGARET MEAD, American Museum of Natural History, New York, N. Y., and HANS LUKAS TEUBER, Department of Neurology, New York University College of Medicine. 251 pages; 24 × 16 cm. 1951. Josiah Macy, Jr. Foundation, New York. Price, $3.50.

Diagnostik und Therapie der Herzinsuffizienz, Kreislauf und Vegetatives System. 16 Fortbildungslehrgang in Bad Nauheim von. 29, September bis 1. Oktober 1950. 111 pages; 24.5 × 17 cm. (paper-bound). 1951. Verlag Von Dr. Dietrich Steinkopff, Darmstadt. Price, brosch. DM 11.-, geb. DM.

Factors Regulating Blood Pressure: Transactions of the Fourth Conference, February 23–24, 1950, New York, N. Y. Edited by BENJAMIN W. ZWEIFACH and EPHRAIM SHORR, Department of Medicine, Cornell University Medical College, New York, N. Y. 219 pages; 23.5 × 15.5 cm. 1951. Sponsored and published by Josiah Macy, Jr. Foundation, New York. Price, $3.00.

Der Genuine Basedow und die Hyperthyreosen und Ihre Behandlung. By DR. MED. ANTON FONIO. 316 pages; 23 × 15.5 cm. (paper-bound). 1951. Verlag Von Dr. Dietrich Steinkopff, Darmstadt. Price, brosch. DM 30,-, geb. DM 32,—.

Handbook of Nutrition: A Symposium Prepared under the Auspices of the Council on Foods and Nutrition of the American Medical Association. 2nd ed. Published for American Medical Association by The Blakiston Company, Philadelphia. 717 pages; 22 × 14.5 cm. 1951. Price, $4.50.

The Human Colon: An Experimental Study Based on Direct Observation of Four Fistulous Subjects. By WILLIAM J. GRACE, M.D., Assistant Professor of Medicine, Cornell University Medical College, New York Hospital, New York; STEWART WOLF, M.D., Associate Professor of Medicine, Cornell University Medical College, New York Hospital, New York, and HAROLD G. WOLFF, M.D., Professor of Medicine (Neurology), Cornell University Medical College, New York Hospital, New York; Foreword by ALAN GREGG, M.D. 239 pages; 24.5 × 16 cm. 1951. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, $7.50.

Immunology. 3d ed. By NOBLE PIERCE SHERWOOD, Ph.D., M.D., F.A.C.P., Professor of Bacteriology, University of Kansas, and Pathologist to the Lawrence Memorial Hospital, Lawrence, Kansas. 731 pages; 22.5 × 14.5 cm. 1951. The C. V. Mosby Company, St. Louis. Price, $8.00.

The Kidney: Medical and Surgical Diseases. By ARTHUR C. ALLEN, M.D., Pathologist, The James Ewing Hospital, etc. 583 pages; 28 × 20.5 cm. 1951. Grune & Stratton, Inc., New York. Price, $15.00.

Medical Treatment: Principles and Their Application. Edited by GEOFFREY EVANS, M.D., F.R.C.P., Consulting Physician, St. Bartholomew's Hospital. 1,464 pages; 25 × 16.5 cm. 1951. Butterworth & Co. (publishers), Ltd., London; The C. V. Mosby Company, St. Louis. Price, $20.00.

Nerve Impulse: Transactions of the First Conference, March 2–3, 1950, New York, N. Y. Editor: DAVID NACHMANSOHN, Department of Neurology, College of Physicians and Surgeons, Columbia University. 159 pages; 23.5 × 15.5 cm. 1951. Josiah Macy, Jr. Foundation, New York. Price, $3.00.

Physicians' Desk Reference to Pharmaceutical Specialties and Biologicals—1951. 5th ed. J. MORGAN JONES, Editor and Publisher; RICHARD R. MAEHLER, Editor, Compilation and Arrangement; H. SHERIDAN BAKETEL, M.D., Professional Editorial Counsel, and RAYMOND J. JAEGGI, Assistant to Editor and Publisher. 632 pages; 26.5 × 18 cm. 1951. Medical Economics, Inc., Rutherford, N. J. Distributed free to physicians.

Primary Carcinoma of the Liver: A Study in Incidence, Clinical Manifestations, Pathology and Etiology. By CHARLES BERMAN, M.D., B.Ch. Rand., Senior Medical Officer, Consolidated Main Reef Mines and Estate, Ltd., Maraisburg, Transvaal, South Africa; with a Foreword by SIR ERNEST KENNAWAY, M.D. Oxon., D.Sc. Lond., F.R.S., F.R.C.P., Late Director, Chester Beatty Research Institute, Royal Cancer Hospital, London, etc.; and an Introduction by HENRY GLUCKMAN, M.R.C.S. Eng., L.R.C.P. Lond., Former Minister of Health, Union of South Africa. Produced by means of a grant from the South African Council for Scientific and Industrial Research. 164 pages; 25.5 × 19 cm. 1951. H. K. Lewis & Co., Ltd., London. Price, 35/- net (price in Great Britain).

Problems of Consciousness: Transactions of the First Conference, March 20–21, 1950, New York, N. Y. Edited by HAROLD A. ABRAMSON, M.D., Department of Physiology, College of Physicians and Surgeons, Columbia University, New York, N. Y. 200 pages; 23.5 × 15.5 cm. 1951. Sponsored and published by Josiah Macy, Jr. Foundation, New York. Price, $3.00.

Problems of Infancy and Childhood: Transactions of the Fourth Conference, March 6–7, 1950, New York, N. Y. Edited by MILTON J. E. SENN, M.D., Departments of Pediatrics and Psychiatry, School of Medicine, Yale University, New Haven, Conn. 181 pages; 23.5 × 15.5 cm. 1951. Sponsored and published by the Josiah Macy, Jr. Foundation, New York. Price, $2.25.

St. Thomas's Reports—Second Series, Vol. VI. Editorial Committee: DR. J. H. CYRIAX, DR. H. K. GOADBY, MR. R. W. NEVIN, DR. J. S. RICHARDSON, DR. R. B. K. RICKFORD, and DR. H. J. WALLACE. 285 pages; 25.5 × 15.5 cm. 1950. St. Thomas's Hospital, London. Price, 10s. 6d.

Spezielle Pathologie der Krankheiten des Zentralen und Peripheren Nervensystems. By DR. GERD PETERS. 437 pages; 24.7 × 17 cm. 1951. Georg Thieme Verlag. Stuttgart; Agents for U. S. A.: Grune & Stratton, New York. Price, Ganzleinen DM 56.—.

Les Stimulines Hypophysaires. By ANDRÉ LEMAIRE, FLORIAN DELBARRE and J. P. MICHARD. 174 pages; 25 × 17 cm. (paper-bound). 1951. Masson et Cie, Paris. Price, 750 fr.

Syllabus of Human Neoplasms. By R. M. MULLIGAN, M.D., Professor of Pathology in the University of Colorado School of Medicine. 317 pages; 26.5 × 18 cm. 1951. Lea & Febiger, Philadelphia. Price, $7.50.

A Textbook of Medicine. 8th ed. Edited by RUSSELL L. CECIL, M.D., Sc.D., Professor of Clinical Medicine Emeritus, Cornell University, New York, and ROBERT F. LOEB, M.D., Bard Professor of Medicine, Columbia University, New York;

Associate Editors: ALEXANDER B. GUTMAN, M.D., Professor of Medicine, Columbia University, New York; WALSH MCDERMOTT, M.D., Associate Professor of Medicine, Cornell University, New York, and HAROLD G. WOLFF, M.D., Associate Professor of Medicine (Neurology), Cornell University. 1627 pages; 26 × 18 cm. 1951. W. B. Saunders Company, Philadelphia. Price, $12.00.

Tomorrow's Horizon in Public Health: Transactions of the 1950 Conference of the Public Health Association of New York City. 109 pages; 23 × 15 cm. (paperbound). 1950. Public Health Association of New York City, New York, N. Y. Price, $1.00.

Veterans Administration Conference on Cortisone Research: A Symposium, August 15 and 16, 1950, Washington, D. C. 120 pages; 27.5 × 21.5 cm. 1951. Merck & Co., Inc., Rahway, New Jersey. Price, None given.

Veterans Administration Technical Bulletins, Series 10, Volume IV, 1950. 142 pages; 27 × 20.5 cm. 1951. Veterans Administration, Washington 25, D. C. Price: Not for sale—limited edition for distribution to VA hospitals and medical libraries.

ANNOUNCEMENT OF NEW JOURNALS

Zeitschrift für Psychotherapie und medizinische Psychologie. Editor: E. KRETSCHMER, Tübingen; Associate Editors: F. MAUZ, Hamburg, and G. KÜHNEL, Göttingen. Publisher: Georg Thieme Verlag, Stuttgart.

COLLEGE NEWS NOTES

A.C.P. Postgraduate Courses, Autumn, 1951

The detailed Postgraduate Bulletin will be published and delivered during July to all members of the College and to non-members, who have requested that their names be placed on the mailing list.

Among courses that are being repeated from some previous year are the following:

Course No. 1, INTERNAL MEDICINE: SELECTED TOPICS; University of Cincinnati College of Medicine; M. A. Blankenhorn, M.D., F.A.C.P., Director; September 17–21.

Course No. 4, CLINICAL NEUROLOGY; Jefferson Medical College of Philadelphia; Bernard J. Alpers, M.D., F.A.C.P., Director; October 29–November 3.

Course No. 7, RECENT ADVANCES IN THE DIAGNOSIS AND TREATMENT OF CARDIOVASCULAR DISEASE; Massachusetts General Hospital; Howard B. Sprague, M.D., F.A.C.P., and Edward F. Bland, M.D., F.A.C.P., Co-directors; November 12–17.

Course No. 9, PHYSIOLOGICAL BASIS FOR INTERNAL MEDICINE; University of Pennsylvania Graduate School of Medicine; Julius H. Comroe, Jr., M.D., F.A.C.P., Director; December 10–15.

Among new courses on the schedule, not previously given by the College, are the following:

Course No. 2, INTERNAL MEDICINE: SELECTED SUBJECTS; Marquette University School of Medicine, Milwaukee, Wis.; Maurice Hardgrove, M.D., F.A.C.P., Director; October 8–13.

Course No. 3, DIAGNOSIS AND TREATMENT OF CARDIOVASCULAR DISEASE; Frank E. Bunts Educational Institute of the Cleveland Clinic Foundation; A. Carlton Ernstene, M.D., F.A.C.P., Director; October 22–27.

Course No. 5, ELECTROCARDIOGRAPHY; Emory University School of Medicine, Atlanta, Ga.; R. Bruce Logue, M.D., F.A.C.P., Director; October 29–November 3.

Course No. 6, GASTRO–ENTEROLOGY; Tulane University of Louisiana School of Medicine, New Orleans, La.; Gordon McHardy, M.D., F.A.C.P., Director; November 12–17.

Course No. 8, CARDIOVASCULAR DISEASES; University of Texas Medical Branch, Galveston, Tex.; George R. Herrmann, M.D., F.A.C.P., Director; December 10–15.

Following are the complete details of courses 1, 2 and 3.

COURSE NO. 1—INTERNAL MEDICINE: SELECTED TOPICS

(September 17–21, 1951)

UNIVERSITY OF CINCINNATI COLLEGE OF MEDICINE
CINCINNATI, OHIO

M. A. Blankenhorn, M.D., F.A.C.P., *Director*

(Minimal Registration, 20;
Maximal Registration, 40)

Fees: A.C.P. Members, $30.00
Non-members, $60.00

OFFICERS OF INSTRUCTION

(All members of the faculty of the University of Cincinnati College of Medicine.)

NATHAN ABRAMS, M.D., Instructor in Medicine.
GEORGE ACHESON, M.D., Professor of Pharmacology.
CHARLES D. ARING, M.D., Professor of Neurology.
J. PARK BIEHL, M.D., Instructor in Medicine.
M. A. BLANKENHORN, M.D., F.A.C.P., Professor of Medicine.
JOHN R. BRAUNSTEIN, M.D., Assistant Professor of Medicine.
ALBERT BRUST, M.D., Assistant Professor of Medicine.
STANLEY DORST, M.D., Associate Professor of Medicine and Dean of the College of Medicine.
VIRGINIA ESSELBORN, M.D., Assistant Professor of Medicine.
BENJAMIN FELSON, M.D., Associate Professor of Radiology.
EUGENE B. FERRIS, M.D., F.A.C.P., Professor of Medicine.
NOBLE O. FOWLER, M.D., Assistant Professor of Medicine.
EDWARD A. GALL, M.D., Professor of Pathology.
JOSEPH N. GANIM, M.D., F.A.C.P., Assistant Professor of Medicine.
HELEN I. GLUECK, M.D., Assistant Professor of Medicine.
LEON GOLDMAN, M.D., Professor of Dermatology and Syphilology.
RICHARD GOLDSMITH, M.D., Instructor in Medicine.
MORTON HAMBURGER, M.D., Associate Professor of Medicine.
ROBERT A. KEHOE, M.D., Professor of Industrial Medicine.
HARVEY KNOWLES, M.D., Instructor in Medicine.
J. HAROLD KOTTE, M.D., F.A.C.P., Assistant Professor of Medicine.
JOHNSON MCGUIRE, M.D., F.A.C.P., Associate Professor of Medicine.
JOHN MUELLER, M.D., Instructor in Medicine.
MORTON REISER, M.D., Assistant Professor of Medicine and Psychiatry.
LEON SCHIFF, M.D., F.A.C.P., Associate Professor of Medicine.
HAROLD S. SCHIRO, M.D., F.A.C.P., Assistant Professor of Medicine.
NATHAN SHAPIRO, M.D., Assistant Clinical Professor of Medicine.
CECIL STRIKER, M.D., F.A.C.P., Assistant Clinical Professor of Medicine.
RICHARD W. VILTOR, M.D., F.A.C.P., Associate Professor of Medicine.
CARL I. WYLER, M.D., F.A.C.P., Instructor in Medicine.
ALBERT ZOSS, M.D., Assistant in Medicine.

The aim of this postgraduate course is to provide discussion of certain aspects of Internal Medicine with particular emphasis upon pathological physiology. In general, the program will consist of morning lectures and a period of ward rounds in smaller groups, and afternoon lectures followed by a conference in which informal discussion will be encouraged. Recent advances in diagnosis and treatment will be stressed.

The subject matter as a whole has been arranged so that it may provide a refresher course for physicians who have had little time in recent years to attend postgraduate courses. Most of the speakers have been active in investigation of the subjects they will discuss.

On Monday, Tuesday, Wednesday and Thursday evenings there will be informal demonstrations and discussions of work in progress in the laboratories for clinical research of the Department of Medicine. Attendance at these evening meetings will be optional. All activities are in the Cincinnati General Hospital. Lectures will be held in the new Mont Reid Pavilion which is air-cooled.

Opportunity will be provided for those interested to visit the Kettering Laboratory of Applied Physiology and the various special research laboratories in the Department of Medicine, University of Cincinnati. The Libraries of the College of Medicine and of the Cincinnati General Hospital will be available to registrants of the course.

Hotel Accommodations: Apply directly to Miss Mary M. Hesse, Director of Sales, Netherland Plaza Hotel, Cincinnati 2, Ohio. Single room, $4.00 daily; double room with double bed, $7.50; twin-bedded room, $9.50 daily. Registrants are urged to arrange their accommodations as early as possible, identifying themselves with the American College of Physicians and this course.

Outline of Course

Mont Reid Pavilion, Cincinnati General Hospital

Monday, September 17

A.M. Session

9:00– 9:30	Registration.
9:30–10:30	Diagnosis and Treatment of the "Spotted Fevers." Dr. Blankenhorn.
10:30–11:00	Leptospiral Infections. Dr. Hamburger.
11:00–12:00	Ward Rounds.
12:00	Lunch.

P.M. Session

1:15– 2:00	Treatment of Anemia Based on the Physiology of Red Blood Cell Formation. Dr. Vilter.
2:00– 2:30	Recent Developments in the Diagnosis and Treatment of Thrombocytopenic Purpura. Dr. Mueller.
2:30– 3:00	Tests for Bleeding and Clotting Phenomena in the Hemorrhagic Diseases. Dr. Schiro.
3:00– 3:30	The Use of Tolserol in the Control of Convulsions in Tetanus. Dr. Biehl.
3:30– 5:00	Conference on Hematology. Dr. Vilter, *Presiding.*
7:00	Informal Dinner for Postgraduate Students and Faculty.

Tuesday, September 18

A.M. Session

9:00–10:00	Newer Diagnostic and Therapeutic Measures in Cardiology. Dr. McGuire.

10:00–10:30 The Use of the Electrocardiogram in the Control of Drug Therapy.
DR. KOTTE.
10:30–11:00 The Practical Value of the Ballistocardiogram in Internal Medicine.
DR. BRAUNSTEIN.
11:00–12:00 Ward Rounds.
12:00 Lunch.

P.M. Session
1:15– 1:30 Clinical Application of Studies of the Pulmonary Circulation in Various Types of Heart and Lung Disease.
DR. FOWLER.
1:30– 2:00 Newer Technics in Roentgen Diagnosis of Cardiovascular Disease.
DR. FELSON.
2:00– 2:45 The Present Status of Anticoagulant Therapy of Myocardial Infarction —The Experience of the Past Five Years.
DR. GLUECK.
2:45– 3:30 The Changing Picture of Subacute Bacterial Endocarditis.
DR. HAMBURGER.
3:30– 5:00 Conference on Cardiovascular Disease.
DR. McGUIRE, *Presiding.*

Wednesday, September 19

A.M. Session
9:00– 9:45 Technics in the Use of Newer Insulins.
DR. STRIKER.
9:45–10:30 Recent Advances in Physiology and Treatment of Diabetic Acidosis.
DR. KNOWLES.
10:30–11:00 The Uses and Abuses of Estrogens in Internal Medicine.
DR. ESSELBORN.
11:00–12:00 Ward Rounds.
12:00 Lunch.

P.M. Session
1:15– 2:00 Dangerous Neurological Habits.
DR. ARING.
2:00– 2:30 Antabuse—A Technic in the Treatment of Alcoholism.
DR. WYLER.
2:30– 3:00 Psychological Factors in Cardiovascular Disease.
DR. REISER.
3:00– 3:30 The Pharmacology of the Newer Drugs Used in the Treatment of Pain.
DR. ACHESON.
3:30– 5:00 Clinical Pathological Conference.
DRS. BLANKENHORN AND GALL.

Thursday, September 20

A.M. Session
9:00–10:00 Differential Diagnosis of Jaundice.
DR. SCHIFF.
10:00–10:45 Hemorrhage from the Upper Alimentary Tract.
DR. SHAPIRO.
10:45–11:00 Treatment of Hepatic Coma.
DR. GANIM.
11:00–12:00 Ward Rounds.
12:00 Lunch.

P.M. Session

1:15– 2:00 The Management of Severe Asthma.
Dr. Dorst.

2:00– 3:00 Industrial Problems in Internal Medicine.
Dr. Kehoe.

3:00– 3:30 Needle Biopsy of the Liver.
Dr. Gall.

3:30– 5:00 Conference on Gastro-enterology.
Dr. Schiff, *Presiding.*

Friday, September 21

A.M. Session

9:00–10:00 Diagnostic and Prognostic Evaluation of Hypertension.
Dr. Ferris.

10:00–11:00 General and Specific Measures in the Management of Essential Hypertension, Benign and Malignant.
Dr. Brust.

11:00–12:00 Ward Rounds.

12:00 Lunch.

P.M. Session

1:15– 2:00 The Diagnostic and Therapeutic Use of I^{131} in Diseases of the Thyroid Gland.
Dr. Goldsmith.

2:00– 3:00 The Present Status of the Treatment of Rheumatoid Arthritis.
Dr. Abrams.

3:00– 3:30 Complications Following the Use of ACTH and Cortisone.
Dr. Brust.

3:30– 5:00 Conference on ACTH and Cortisone.
Dr. Ferris, *Presiding.*

COURSE NO. 2—INTERNAL MEDICINE: SELECTED SUBJECTS

(October 8–13, 1951)

Marquette University School of Medicine
Milwaukee, Wis.

Maurice Hardgrove, M.D., F.A.C.P., *Director*

(Maximal Registration, 35)

Fees: A.C.P. Members, $30.00
Non-members, $60.00

Advisory Council

Francis D. Murphy, M.D., F.A.C.P.
Frederick W. Madison, M.D., F.A.C.P.
John S. Hirschboeck, M.D., F.A.C.P.
William M. Jermain, M.D., F.A.C.P.
Joseph W. Rastetter, M.D., F.A.C.P.

Officers of Instruction

W. A. Douglas Anderson, M.D., F.A.C.P., Professor and Director of Department of Pathology, Marquette University School of Medicine; Member, Graduate School Faculty.

ARMIN R. BAIER, M.D., Clinical Instructor in Medicine, Marquette University School of Medicine.

ANDREW L. BANYAI, M.D., F.A.C.P., Associate Clinical Professor of Medicine, Marquette University School of Medicine; Clinical Director, Muirdale Sanitarium.

HARRY BECKMAN, M.D., Professor and Director of Department of Pharmacology, Marquette University School of Medicine; Member, Graduate School Faculty.

ELEXIOUS T. BELL, M.D., Professor of Pathology, University of Minnesota Medical School, Minneapolis, Minn.

DANIEL B. CLAUDON, M.D., Associate in Pediatrics, Marquette University School of Medicine; Assistant Director of Laboratories, Columbia Hospital and Milwaukee Children's Hospital; Chief of Hematology Service, Milwaukee Children's Hospital.

MANDRED W. COMFORT, M.D., F.A.C.P., Professor of Medicine, University of Minnesota (Mayo Foundation); Associate in Medicine, Mayo Clinic; Rochester, Minn.

HOWARD L. CORRELL, M.D., F.A.C.P., Assistant Clinical Professor of Medicine, Marquette University School of Medicine; Coordinator of Cardiovascular Section.

RICHARD V. EBERT, M.D., F.A.C.P., Clinical Associate Professor of Medicine, University of Minnesota Medical School; Chief of Medical Service, Veterans Administration Hospital; Minneapolis, Minn.

WILLIAM W. ENGSTROM, M.D., Assistant Professor of Medicine, Marquette University School of Medicine.

EDITH B. FARNSWORTH, M.D., Associate in Medicine, Northwestern University Medical School, Chicago, Ill.

EDMUND B. FLINK, M.D., Associate Professor of Medicine, University of Minnesota Medical School, Minneapolis, Minn.

ROBERT A. FRISCH, M.D., F.A.C.P., Assistant Clinical Professor of Medicine, Marquette University School of Medicine.

JOSEPH W. GALE, M.D., F.A.C.S., Professor of Surgery, University of Wisconsin Medical School, Madison, Wis.

MARK W. GARRY, M.D., F.A.C.P., Assistant Clinical Professor of Medicine, Marquette University School of Medicine; Chief of Medical Service, Veterans Administration Hospital, Wood, Wis.

JOHN L. GARVEY, M.D., F.A.C.P., Clinical Professor and Director of Division of Neurology, Marquette University School of Medicine.

EDGAR S. GORDON, M.D., F.A.C.P., Associate Professor of Medicine, University of Wisconsin Medical School, Madison, Wis.

TIBOR J. GREENWALT, M.D., F.A.C.P., Assistant Clinical Professor of Medicine, Marquette University School of Medicine; Medical Director, Junior League Blood Center of Milwaukee.

NATHAN GROSSMAN, M.D., Clinical Instructor in Medicine, Marquette University School of Medicine.

MAURICE HARDGROVE, M.D., F.A.C.P., Associate Clinical Professor of Medicine, Marquette University School of Medicine; Member, Graduate School Faculty.

JOHN S. HIRSCHBOECK, M.D., F.A.C.P., Dean and Associate in Physiology and Medicine, Marquette University School of Medicine.

DWIGHT J. INGLE, Ph.D., Senior Research Scientist, Upjohn Research Laboratories, Kalamazoo, Mich.

WILLIAM M. JERMAIN, M.D., F.A.C.P., Associate Clinical Professor of Medicine, Marquette University School of Medicine.

CHESTER M. KURTZ, M.D., F.A.C.P., Associate Professor of Medicine, University of Wisconsin Medical School, Madison, Wis.

Joseph F. Kuzma, M.D., Assistant Professor of Pathology, Marquette University School of Medicine; Member, Graduate School Faculty; Director of Laboratories, Milwaukee County Hospital.

Louis R. Limarzi, M.D., F.A.C.P., Associate Professor of Medicine, University of Illinois College of Medicine, Chicago, Ill.

M. C. F. Lindert, M.D., F.A.C.P., Assistant Clinical Professor of Medicine, Marquette University School of Medicine.

Joseph M. Lubitz, M.D., F.A.C.P., Assistant Professor of Pathology, Marquette University School of Medicine; Director of Laboratories, Veterans Administration Hospital, Wood, Wis.

Mischa J. Lustok, M.D., F.A.C.P., Assistant Clinical Professor of Medicine, Marquette University School of Medicine.

Frederick W. Madison, M.D., F.A.C.P., Associate Clinical Professor of Medicine, Marquette University School of Medicine.

William S. Middleton, M. D., F.A.C.P., Dean and Professor of Medicine, University of Wisconsin Medical School, Madison, Wis.

S. Archibald Morton, M.D., Clinical Professor and Director of the Department of Radiology, Marquette University School of Medicine; Member, Graduate School Faculty.

Francis D. Murphy, M.D., F.A.C.P., Clinical Professor and Director of the Department of Medicine, Marquette University School of Medicine; Member, Graduate School Faculty.

Timothy R. Murphy, M.D., Clinical Instructor in Medicine, Marquette University School of Medicine.

George C. Owen, M.D., F.A.C.P., Associate in Medicine, Marquette University School of Medicine.

Walter L. Palmer, M.D., F.A.C.P., Professor of Medicine, University of Chicago School of Medicine, Chicago, Ill.

S. B. Pessin, M.D., Associate Professor of Pathology, Marquette University School of Medicine; Member, Graduate School Faculty.

Ray Piaskoski, M.D., Assistant Clinical Professor of Medicine, Marquette University School of Medicine; Chief of Physical Medicine and Rehabilitation, Veterans Administration Hospital, Wood, Wis.

H. Marvin Pollard, M.D., F.A.C.P., Associate Professor of Medicine, University of Michigan Medical School, Ann Arbor, Mich.

Karver L. Puestow, M.D., F.A.C.P., Professor of Clinical Medicine, University of Wisconsin Medical School, Madison, Wis.

Armand J. Quick, M.D., Professor and Director of the Department of Biochemistry, Marquette University School of Medicine; Member, Graduate School Faculty.

Joseph W. Rastetter, M.D., F.A.C.P., Assistant Clinical Professor of Medicine, Marquette University School of Medicine; Director, Milwaukee Cancer Diagnostic Clinic.

Gorton Ritchie, M.D., Director of Laboratories, Columbia Hospital and Milwaukee Children's Hospital.

Francis F. Rosenbaum, M.D., F.A.C.P., Assistant Clinical Professor of Medicine, Marquette University School of Medicine.

O. A. Sander, M.D., F.A.C.P., Associate in Medicine, Marquette University School of Medicine.

C. Morrison Schroeder, M.D., F.A.C.S., Assistant Clinical Professor of Surgery, Marquette University School of Medicine.

Joseph Shaiken, M. D., Assistant Clinical Professor of Medicine, Marquette University School of Medicine.

THEODORE L. SQUIER, M.D., F.A.C.P., Associate Clinical Professor of Medicine, Marquette University School of Medicine.

JOHN D. STEELE, JR., M.D., F.A.C.S., Assistant Clinical Professor of Surgery, Marquette University School of Medicine.

WILLARD O. THOMPSON, M.D., F.A.C.P., Clinical Professor of Medicine, University of Illinois College of Medicine; Managing Editor, "Clinical Endocrinology"; Chicago, Ill.

DONALD M. WILLSON, M.D., F.A.C.P., Assistant Clinical Professor of Medicine, Marquette University School of Medicine.

The selection of subjects and faculty for the course is based on the desire to present both preclinical and clinical viewpoints.

Grouping of disorders of the body systems will provide an opportunity for teachers with special experience to discuss their assigned material. Case studies and patient presentations will be included in conjunction with many of the sessions. The last hour of each morning and afternoon will be devoted to a question and answer period or a round table in which the faculty will take part.

All sessions will be held in the medical school building, which houses the library of the Medical School and the Milwaukee Academy of Medicine. The library is open in the evening. The school is within walking or easy transportation distance of the hotels.

For those who wish to attend clinico-pathological conferences, lectures or make ward rounds on Saturday, October 13, facilities will be available on the various services of the Milwaukee County Hospital and the Veterans Administration Hospital (Wood).

Hotel Accommodations: Hotel Schroeder, Milwaukee 3, Wis., Mr. O. M. Petterson, Assistant Manager. Single rooms, $4.00 to $8.00; double rooms, $6.50 to $10.00; twin-bedded rooms, $8.50 to $12.00. Make application direct, identifying yourself with the American College of Physicians and this course.

OUTLINE OF COURSE

HEMATOLOGY

Monday, October 8

A.M. Session

9:00	Registration.
9:15– 9:30	Welcome. DR. HIRSCHBOECK.
9:30–10:00	Physiology of the Blood Clotting Mechanism. DR. QUICK.
10:00–10:30	Prothrombin Physiology and Deficient States. DR. QUICK.
10:30–10:45	Intermission.
10:45–11:30	Diagnostic and Therapeutic Aspects of Multiple Myeloma. DR. LIMARZI.
11:30	Question and Discussion Period.

The group will visit the Junior League Blood Center of Milwaukee and its Research Unit, 763 North 18th Street, during the noon hour.

DR. GREENWALT.

P.M. Session

2:00– 2:30 Blood Viscosity.
Dr. Hirschboeck.

2:30– 3:00 Purpura.
Dr. Madison.

3:00– 3:15 Intermission.

3:15– 3:45 Hemato-allergic Manifestations.
Dr. Squier.

3:45– 4:15 The Treatment of Acute Leukemias in Children.
Dr. Claudon.

4:15– 4:45 Immuno-hematology.
Dr. Greenwalt.

4:45 Question and Discussion Period.

7:30 Hematology Seminar.
Drs. Anderson and Pessin.

Cardiovascular Renal Disorders

Tuesday, October 9

A.M. Session

9:00– 9:45 Some Aspects of the Physiology of Heart Failure.
Dr. Grossman.

9:45–10:15 Unipolar Limb Leads.
Dr. Rosenbaum.

10:15–10:30 Intermission.

10:30–11:00 Acute Cardiac Emergencies.
Dr. Kurtz.

11:00–11:30 Treatment of Subacute Bacterial Endocarditis.
Dr. Correll.

11:30 Question and Discussion Period.

The Radioisotope Unit of the Medical School will be visited during the noon hour.
Dr. Hirschboeck.

P.M. Session

2:00– 2:45 Genesis of Edema.
Dr. Flink.

2:45– 3:15 Treatment of Edema.
Dr. Farnsworth.

3:15– 3:30 Intermission.

3:30– 4:15 Glomerular and Tubular Diseases of the Kidney.
Dr. Bell.

4:15– 5:00 Treatment of Nephritis.
Dr. F. D. Murphy.

5:00 Question and Discussion Period.

7:30 A demonstration of the artificial kidney.
Drs. Willson, T. R. Murphy and Baier.

Cardiovascular Renal Disorders (*continued*)

Wednesday, October 10

A.M. Session

9:00– 9:30 Clinical Aspects of Potassium Metabolism.
Dr. Engstrom.

9:30–10:00 Pathological Report on Congenital Cardiovascular Disorders.
Dr. Ritchie.
10:00–10:15 Intermission.
10:15–10:45 Cardiac Catheterization.
Dr. Grossman.
10:45–11:30 Surgical Treatment of Congenital Cardiovascular Anomalies.
Dr. Gale.
11:30 Question and Discussion Period.

The group will visit the Cardiac Catheterization Unit, Milwaukee County Dispensary, 2430 West Wisconsin Avenue, during the noon hour.
Dr. Grossman.

Metabolic Disorders

P.M. Session
2:00 2:45 Rôle of Adrenal Cortex in Hemostasis.
Dr. Ingle.
2:45– 3:15 Methods of Evaluating Adrenal Cortical Function.
Dr. Engstrom.
3:15– 3:30 Intermission.
3:30– 4:15 Examples of Adrenal Dysfunction.
Dr. Thompson.
4:15– 5:00 Clinical Application of ACTH and Cortisone.
Dr. Gordon.
5:00 Question and Discussion Period
6:30 Social Hour—Milwaukee Internists' Club at Milwaukee University Club, 924 East Wells Street.

Gastro-Enterology

Thursday, October 11

A.M. Session
9:00– 9:45 A Discussion of Pancreatic Disorders.
Dr. Comfort.
9:45–10:15 Surgical Treatment of Pancreatic Disorders.
Dr. Schroeder.
10:15–10:30 Intermission.
10:30–11:00 Disturbances in Liver Physiology as Measured by Laboratory Methods.
Dr. Lubitz.
11:00–11:30 Treatment of Acute and Chronic Hepatitis.
Dr. Lindert.
11:30 Question and Discussion Period.

During the noon hour rounds will be made on the Rehabilitation Wards (Arthritis) at Veterans Administration Hospital, Wood, Wisconsin.
Drs. Garry and Piaskoski.

P.M. Session
2:00– 2:45 Diagnosis and Treatment of Gastric Lesions.
Dr. Palmer.
2:45– 3:15 Tumors of Small Bowel.
Dr. Shaiken.

3:15– 3:30 Intermission.
3:30– 4:00 Some Aspects of Bowel Physiology.
Dr. Puestow.
4:00– 4:45 Management of Small and Large Bowel Inflammatory Lesions.
Dr. Pollard.
4:45 Question and Discussion Period.
6:30 Dinner for those attending course will be sponsored by Marquette University School of Medicine. Dr. William S. Middleton, Speaker and Guest of Honor. Milwaukee University Club, 924 East Wells Street.

Chest Diseases

Friday, October 12

A.M. Session
9:00– 9:45 Practical Application of Respiratory Function Studies.
Dr. Ebert.
9:45–10:15 Bronchoscopy and Bronchography in the Investigation of Pulmonary Lesions.
Dr. Steele.
10:15–10:30 Intermission.
10:30–11:15 Differential Diagnosis of Pulmonary Lesions.
Dr. Banyai.
11:15–11:45 Chronic Berylliosis.
Dr. Sander.
11:45 Question and Discussion Period.
The group will visit the Veterans Administration Hospital, Wood, respiratory function unit during the noon hour.
Dr. Owen.

P.M. Session
2:00– 2:30 Use of Antibiotics in Non-tuberculous Inflammatory Lung Diseases.
Dr. Jermain.
2:30– 3:15 Roentgenological Manifestations of Diseases of the Pleura and Bronchi.
Dr. Morton.
3:15– 3:30 Intermission.
3:30– 4:30 Not in the Thing Itself.
Dr. Beckman.
4:30 Question and Discussion Period.

Saturday, October 13

For those who wish to make rounds on Saturday morning, the following are recommended:

Veterans Administration Hospital, Wood, Wis.
Ward Rounds and Conferences:
Gastro-enterology—Dr. Lindert—9:00 A.M.
Cardiology—Dr. Lustok and Dr. Frisch—9:00 A.M.
Arthritis—Dr. Garry—9:00 A.M.
Student Conference—Dr. Hardgrove—9:00 A.M.
Chest Conference—Dr. Owen—10:00 A.M.
Clinico-Pathological Conference—Dr. Lubitz—11:00 A.M.

Milwaukee County Hospital
Ward Rounds and Conferences:
General Medicine—Dr. F. D. Murphy—9:00 A.M.
Metabolism—Dr. Engstrom—9:00 A.M.
Neurology—Dr. Garvey—9:00 A.M.
Cardiac Seminar—Dr. Rosenbaum—10:00 A.M.
Clinico-Pathological Conference—Dr. Kuzma—11:00 A.M.

COURSE NO. 3—THE DIAGNOSIS AND TREATMENT OF CARDIOVASCULAR DISEASE

(October 22–27, 1951)

Frank E. Bunts Educational Institute of the Cleveland Clinic Foundation
Euclid Avenue at East 93rd Street, Cleveland 6, Ohio

A. Carlton Ernstene, M.D., F.A.C.P., *Director*

(Minimal Registration, 50;
Maximal Registration, 100)

Fees: A.C.P. Members, $30.00
Non-members, $60.00

Consulting Committee

Donald B. Effler, M.D.
William J. Engel, M.D., F.A.C.S.
Donald E. Hale, M.D.
Stanley O. Hoerr, M.D., F.A.C.S.
Harold R. Rossmiller, M.D., F.A.C.P.
Robert W. Schneider, M.D., F.A.C.P.
Robert D. Taylor, M.D., F.A.C.P.
Walter J. Zeiter, M.D.

Officers of Instruction

Charles P. Bailey, M.D., F.A.C.S., Professor of Thoracic Surgery, Hahnemann Medical College and Hospital of Philadelphia, Philadelphia, Pa.
John D. Battle, M.D., F.A.C.P., Department of Medicine, Cleveland Clinic.
Claude S. Beck, M.D., F.A.C.S., Professor of Cardiovascular Surgery, Western Reserve University School of Medicine.
E. N. Collins, M.D., F.A.C.P., Head, Department of Gastro-enterology, Cleveland Clinic.
Arthur C. Corcoran, M.D., Assistant Director, Research Division, Cleveland Clinic.
George Crile, Jr., M.D., F.A.C.S., Department of Surgery, Cleveland Clinic.
Victor G. deWolfe, M.D., Department of Cardiovascular Disease, Cleveland Clinic.
John H. Dingle, M.D., Professor of Preventive Medicine, Western Reserve University School of Medicine.
Robert S. Dinsmore, M.D., F.A.C.S., Chief of Staff, Division of Surgery, Cleveland Clinic.
Donald B. Effler, M.D., Department of Thoracic Surgery, Cleveland Clinic.
A. Carlton Ernstene, M.D., F.A.C.P., Chief of Staff, Division of Medicine, Cleveland Clinic.

HAROLD FEIL, M.D., F.A.C.P., Clinical Professor of Medicine, Western Reserve University School of Medicine.
W. JAMES GARDNER, M.D., F.A.C.S., Head, Department of Neurological Surgery, Cleveland Clinic.
JOHN R. HASERICK, M.D., Department of Dermatology and Syphilology, Cleveland Clinic.
JOHN B. HAZARD, M.D., Head, Department of Pathology, Cleveland Clinic.
HERMAN K. HELLERSTEIN, M.D., Clinical Instructor in Medicine, Western Reserve University School of Medicine.
STANLEY O. HOERR, M.D., F.A.C.S., Department of Surgery, Cleveland Clinic.
C. ROBERT HUGHES, M.D., Head, Department of Roentgenology, Cleveland Clinic.
DAVID O. HUMPHREY, M.D., Department of Cardiovascular Disease, Cleveland Clinic.
EDWARD M. KLINE, M.D., F.A.C.P., Instructor in Medicine, Western Reserve University School of Medicine.
WILHELM J. KOLFF, M.D., Research Division, Cleveland Clinic.
FAY A. LEFEVRE, M.D., F.A.C.P., Department of Cardiovascular Disease, Cleveland Clinic.
LEONARD L. LOVSHIN, M.D., Department of Medicine, Cleveland Clinic.
JOHN W. MARTIN, JR., M.D., F.A.C.P., Instructor in Medicine, Western Reserve University School of Medicine.
E. PERRY MCCULLAGH, M.D., F.A.C.P., Head, Department of Endocrinology and Metabolism, Cleveland Clinic.
EARL W. NETHERTON, M.D., Head, Department of Dermatology and Syphilology, Cleveland Clinic.
ARTHUR D. NICHOL, M.D., F.A.C.P., Director of the Medical Service, St. Luke's Hospital.
IRVINE H. PAGE, M.D., F.A.C.P., Director, Research Division, Cleveland Clinic.
WILLIAM L. PROUDFIT, M.D., F.A.C.P., Department of Cardiovascular Disease, Cleveland Clinic.
CHARLES H. RAMMELKAMP, M.D., Professor of Medicine and Associate Professor of Preventive Medicine, Western Reserve University School of Medicine.
A. H. ROBNETT, M.D., Department of Surgery, Cleveland Clinic.
ARTHUR L. SCHERBEL, M.D., Department of Medicine, Cleveland Clinic.
MAURICE A. SCHNITKER, M.D., F.A.C.P., Chief of Medicine, St. Vincent's Hospital, Toledo, Ohio.
ROY W. SCOTT, M.D., F.A.C.P., Professor of Medicine, Western Reserve University School of Medicine; Chief of Medicine, Cleveland City Hospital.
F. MASON SONES, M.D., Department of Cardiovascular Disease, Cleveland Clinic.
ROBERT D. TAYLOR, M.D., F.A.C.P., Research Division, Cleveland Clinic.
RAY A. VAN OMMEN, M.D., Department of Cardiovascular Disease, Cleveland Clinic.
H. SCOTT VANORDSTRAND, M.D., F.A.C.P., Head, Department of Pulmonary Disease, Cleveland Clinic.
RICHARD N. WESTCOTT, M.D., Department of Cardiovascular Disease, Cleveland Clinic.
JOHN F. WHITMAN, M.D., Department of Cardiovascular Disease, Cleveland Clinic.
ROBERT E. WISE, M.D., Department of Roentgenology, Cleveland Clinic.

This course will place emphasis on current concepts of pathologic physiology and recent advances in the diagnosis and treatment of cardiovascular disease. The major forms of cardiac and peripheral vascular disease and their complications will be considered in detail, and there will be discussions also of less frequently encountered conditions. Newer knowledge in electrocardiography and roentgenologic diagnosis will be reviewed, and the surgical treatment of heart disease will be covered in several

presentations. The course will include lectures, clinical demonstrations, and question and answer panels.

The lectures will be given in the Founders' and Staff Room of the Cleveland Clinic.

Hotel Accommodations: Accommodations may be obtained at the Wade Park Manor, East 107th Street and Park Lane, Cleveland 6. Mr. Owen C. Obetz, General Manager. Single rooms, $5.50 to $7.00; twin-bedded rooms, $8.50 to $10.00; suites from $15.00 and up. Reservations should be made direct, identifying yourself with the American College of Physicians and this course.

A reception and dinner will be given for members of the course and their wives at the Wade Park Manor on the first evening, October 22. On the second evening, October 23, the members and their wives will be guests of the General Electric Company Lighting Institute at Nela Park. Busses will leave the Wade Park Manor at 7:15 P.M.

Outline of Course

Monday, October 22

A.M. Session

8:00– 8:50 Registration.
8:50– 9:00 Introductory Remarks and Announcements.
Dr. Ernstene.

Rheumatic Heart Disease and Its Complications

9:00– 9:30 Etiology and Pathogenesis of Rheumatic Fever.
Dr. Dingle.
9:30–10:00 Treatment of Rheumatic Fever.
Dr. Ernstene.
10:00–10:30 Prophylaxis of Rheumatic Fever.
Dr. Rammelkamp.
10:30–10:50 Complications of Rheumatic Heart Disease.
Dr. Ernstene.
10:50–11:00 Intermission.
11:00–11:30 Treatment and Prevention of Bacterial Endocarditis.
Dr. Van Ommen.
11:30–12:00 Resection of the Atrial Appendage. (Motion Picture)
Dr. Hellerstein.
12:00–12:30 Question and Answer Panel.
12:30–1:30 Luncheon—Courtesy of the Cleveland Clinic.

Peripheral Vascular Disease

P.M. Session

1:30– 2:00 Thrombo-Angiitis Obliterans and Arteriosclerosis Obliterans.
Dr. LeFevre.
2:00– 2:30 Raynaud's Disease and the Raynaud's Syndrome.
Dr. Scherbel.
2:30– 2:50 Polyarteritis Nodosa.
Dr. Battle.
2:50– 3:00 Intermission.
3:00– 3:30 Acute Occlusion of Peripheral Arteries.
Dr. deWolfe.
3:30– 4:00 Spontaneous Subarachnoid Hemorrhage.
Dr. Gardner.

4:00– 4:30 Thrombo-embolic Disease.
DRS. LEFEVRE AND CRILE.
4:30– 5:00 Question and Answer Panel.
6:30 Reception and Dinner for Members of the Course and their Wives at the Wade Park Manor.

Tuesday, October 23

A.M. Session
9:00– 9:45 Recent Advances in Electrocardiography.
DR. PROUDFIT.
9:45–10:30 Diagnosis and Treatment of the Cardiac Arrhythmias.
DR. SCHNITKER.
10:30–10:50 Diagnosis and Treatment of Pheochromocytoma.
DR. MCCULLAGH.
10:50–11:00 Intermission.
11:00–11:30 Pericarditis including the Syndrome of Chronic Cardiac Tamponade.
DR. WHITMAN.
11:30–12:00 Systemic Lupus Erythematosus.
DR. HASERICK.
12:00–12:30 Question and Answer Panel.
12:30– 1:30 Luncheon—Courtesy of the Cleveland Clinic.

P.M. Session
1:30– 1:50 Clinical Aspects of Syphilitic Aortitis.
DR. LEFEVRE.
1:50– 2:15 Treatment of Syphilitic Aortitis.
DR. NETHERTON.
2:15– 2:45 The Heart in Hyperthyroidism and Myxedema.
DR. ERNSTENE.
2:45– 3:15 Unusual Forms of Heart Disease.
DR. PROUDFIT.
3:15– 3:30 Intermission.
3:30– 4:00 Syncope in Patients with Heart Disease.
DR. HUMPHREY.
4:00– 4:30 Dissecting Aneurysm of the Aorta.
DR. SCHERBEL.
4:30– 5:00 Question and Answer Panel.
7:30 Visit to the General Electric Lighting Institute, Nela Park.

Wednesday, October 24

A.M. Session
8:00– 9:00 Medical Clinic.
DR. ERNSTENE AND STAFF.

HYPERTENSION

9:00– 9:30 Types of Hypertension and Their Recognition.
DR. TAYLOR.
9:30–10:15 Etiology and Pathogenesis of Essential Hypertension.
DR. PAGE.
10:15–10:40 Renal Function Tests.
DR. CORCORAN.
10:40–10:50 Intermission.
10:50–11:15 Diagnosis and Treatment of Chronic Pyelonephritis.
DR. HUMPHREY.

11:15–12:00 Treatment of Essential Hypertension.
Dr. Taylor.
12:00–12:30 Question and Answer Panel.
12:30– 1:30 Luncheon—Courtesy of the Cleveland Clinic.

P.M. Session
1:30– 2:00 Cardiovascular Roentgenology.
Dr. Hughes.
2:00– 2:20 Angiocardiography and Aortography.
Dr. Wise.
2:20– 2:50 Indications for and Technic of Cardiac Catheterization.
Dr. Sones.
2:50– 3:00 Intermission.
3:00– 3:30 Pulmonary Heart Disease.
Dr. Martin.
3:30– 4:15 Surgical Treatment of Rheumatic Valvular Disease.
Dr. Bailey.
4:15– 4:30 The Artificial Heart.
Dr. Kolff.
4:30– 5:00 Question and Answer Panel.

Thursday, October 25

A.M. Session

Congenital Heart Disease

9:00– 9:30 Diagnosis of Coarctation of the Aorta.
Dr. Proudfit.
9:30–10:00 Surgical Treatment of Coarctation of the Aorta. (Motion Picture)
Dr. Effler.
10:00–10:15 Diagnosis of Patent Ductus Arteriosus.
Dr. Sones.
10:15–10:30 Surgical Treatment of Patent Ductus Arteriosus. (Motion Picture)
Dr. Effler.
10:30–10:45 Intermission.
10:45–11:15 Differential Diagnosis of Cyanotic Types of Congenital Heart Disease.
Dr. Sones.
11:15–12:00 Surgical Treatment of Septal Defects and Cyanotic Types of Congenital Heart Disease.
Dr. Bailey.
12:00–12:30 Question and Answer Panel.
12:30– 1:30 Luncheon—Courtesy of the Cleveland Clinic.

P.M. Session
1:30– 2:00 The Artificial Kidney and the Treatment of Uremia.
Dr. Kolff.
2:00– 2:30 Clinical Use of Anticoagulants.
Dr. deWolfe.
2:30– 2:50 Cardiac Neurosis.
Dr. Lovshin.
2:50– 3:00 Intermission.
3:00– 3.30 The Heart in Pregnancy.
Dr. Feil.
3:30– 4:00 Heart Disease in Relation to Anesthesia and Surgical Operations.
Dr. Ernstene.

4:00– 4:30 Resuscitation of the Heart.
Drs. Dinsmore and Hoerr.
4:30– 5:00 Question and Answer Panel.

Friday, October 26

A.M. Session
8:00– 9:00 Clinicopathological Conference.
Dr. Hazard.

Coronary Heart Disease

9:00– 9:30 Recent Studies on Arteriosclerosis.
Dr. Page.
9:30–10:00 Diagnosis and Treatment of Angina Pectoris.
Dr. Whitman.
10:00–10:30 Diagnosis and Treatment of Acute Myocardial Infarction.
Dr. Scott.
10:30–10:45 Intermission.
10:45–11:15 Complications and Sequelae of Myocardial Infarction.
Dr. Ernstene.
11:15–11:35 Acute Coronary Failure.
Dr. Proudfit.
11:35–12:00 Paroxysmal Cardiac Dyspnea. (Cardiac Asthma).
Dr. Ernstene.
12:00–12:30 Question and Answer Panel.
12:30– 1:30 Luncheon—Courtesy of the Cleveland Clinic.

P.M. Session
1:30– 2:15 Surgical Treatment of Coronary Artery Disease.
Dr. Beck.
2:15– 2:45 The Cardiac Patient in Industry.
Dr. Kline.
2:45– 3:15 Pathogenesis of Congestive Heart Failure.
Dr. Westcott.
3:15– 3:30 Intermission.
3:30– 3:45 Reactions to Mercuhydrin.
Dr. Whitman.
3:45– 4:30 Treatment of Congestive Heart Failure.
Dr. Nichol.
4:30– 5:00 Question and Answer Panel.

Saturday, October 27

A.M. Session
9:00– 9:20 Pulmonary Arteriovenous Fistula.
Dr. VanOrdstrand.
9:20– 9:50 Gastrointestinal Symptoms Related to Cardiovascular Disease.
Dr. Collins.
9:50–10:20 Superior Venal Caval Obstruction and Anomalies of the Aortic Arch System.
Dr. Sones.
10:20–10:30 Intermission.
10:30–11:00 Chronic Venous Insufficiency.
Dr. Robnett.

11:00–11:30 Acute Myocarditis.
Dr. LeFevre.
11:30–12:30 Question and Answer Panel. (A review of the course.)

1951 Directory, American College of Physicians

The Directory of the American College of Physicians is being revised, and new members, elected since the publication of the 1949 Directory, are being added. The Directory is published biennially. In addition to including salient information about the College and its various activities, it includes a complete biographical roster of members and a complete geographical roster of members. The Board of Regents of the College has directed that the Directory be made available to Fellows and Associates at a pre-publication price of $4.00 postpaid. Life Members will receive a copy without charge. Post-publication price will be $5.00.

On or about May 1, the Directory Data forms were mailed to all members and anyone who failed to return his revised biographical data by July 15 will probably be listed in exactly the same manner as in the 1949 Directory. Official order forms have been mailed to all members of the College and each is urged to return his order promptly, if he has not already done so, in order that he may be assured of the pre-publication price of $4.00. Copies of the Directory will be ready for delivery in the late Autumn.

Gifts to the College Library of Publications by Members

The following Fellows of the College have recently presented copies of their new books to the College Library of Publications by Members:

Dr. Burrill B. Crohn, New York, N. Y., "Regional Ileitis."
Dr. Samuel Soskin, Chicago, Ill., "Progress in Clinical Endocrinology."
Dr. William B. Terhune, New Canaan, Conn., "The Integration of Psychiatry and Medicine."
Dr. Walter C. Alvarez, Rochester, Minn., "The Neuroses."

The College Library of Publications by Members is maintained at College Headquarters. Members frequently present copies of their books to the College and thus the library has become a living memorial to the Member-Authors.

New Life Members

The College is gratified to announce that the following Fellows have become Life Members of the American College of Physicians since the publication of the last issue of this journal:

Dr. Aaron Keinigsberg, Chicago, Ill.
Dr. Robert W. Vines, Denver, Colo.

Courses Offered by University of California School of Medicine

The University Extension of the University of California School of Medicine, San Francisco, through the Director of Postgraduate Instruction, Stacy R. Mettier, M.D., F.A.C.P., has announced the following forthcoming course: Psychiatry and Neurology, at the Langley Porter Clinic, ten weeks, August 20–October 26, 1951. Dr. Karl M. Bowman, Professor of Psychiatry, will direct the course which will cover: General psychiatry, child psychiatry, psychobiology, psychoanalysis, psychology

and psychopathology, functional and organic psychoses, psychoneuroses, therapy, psychosomatic problems, neuroanatomy, clinical neurology, neuropathology, neurophysiology, electroencephalography, X-ray diagnosis, cultural anthropology, and other related topics.

The fee, $200.00, is payable in advance. Application forms are available through Stacy R. Mettier, M.D., Medical Extension, University of California Medical Center, San Francisco 22, Calif.

The American Psychosomatic Society will hold its Ninth Annual Meeting in Chicago, March 29–30, 1952. The Program Committee would like to receive titles and abstracts of papers for consideration for the program, by December 1, 1951. The time allotted for the reading of each paper will be twenty minutes. The Committee is interested in investigations in the theory and practice of psychosomatic medicine as applied to adults and children in all the medical specialties, and in contributions in psychophysiology and ecology. Material should be sent, in duplicate, to Dr. Roy R. Grinker, Chairman, 714 Madison Ave., New York 21, N. Y.

Regular Corps Examination for Medical Officers United States Public Health Service

A competitive examination for the appointment of Medical Officers in the Regular Corps of the United States Public Health Service will be held September 4–6, 1951, in various locations throughout the United States. Application forms and additional information may be obtained by writing to the Surgeon General, United States Public Health Service, Federal Security Agency, Washington 25, D. C., Attention: Division of Commissioned Officers. All applications must be received no later than August 6, 1951.

The Medical Film Guild, Ltd., 167 W. 57th St., New York 19, N. Y., offers for review a new sound teaching film, in full color, "Urinary Infections—Bacteriology, Pathology and Treatment." The film requires a forty-one minute showing period. Production of the film was under a grant for postgraduate instruction given by the Nepera Chemical Co., Inc. The initial showing was held in April, 1951, at the Thirty-first Annual Session of the American College of Physicians in St. Louis.

The Department of State has issued a bulletin, "United States Government International Exchange Opportunities," listing such opportunities available under the Fulbright Act. This year nearly 10,000 persons are being exchanged with more than 60 foreign countries for study, teaching, lecturing, and research under the various grant-in-aid programs. The bulletin gives information about opportunities available to United States citizens for graduate study, teaching, lecturing, and advanced research. This bulletin is known as Department of State Publication 4198, and is sold for ten cents per copy by the Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C.

The Wellcome Historical Medical Library makes available to students of the history of medicine and the allied sciences a truly great collection which is unique both in its scope and the conditions which govern its use.

The resources of the Library are freely available to any inquirer. Correspondence relating to the history and bibliography of medicine will be welcomed, and a cordial

invitation to visit The Wellcome Historical Medical Library is extended to all physicians on behalf of The Wellcome Foundation Ltd. and of Burroughs Wellcome & Co. (U.S.A.) Inc. The library is located at 183–193 Euston Rd., London, N.W. 1. Physicians visiting England are also invited to visit a closely allied institution, The Wellcome Historical Medical Museum, 28 Portman Sq., London.

The National Institutes of Health and the National Cancer Institute have recently published two booklets, "Cancer of the Skin," and "Cancer of the Genito-urinary Tract," each based on the contention that most cancer can be cured if found, diagnosed and treated early. It is apparent these publications are intended primarily for the laity. By the National Cancer Institute, in cooperation with the American Cancer Society, they both carry the keynote, "see a doctor . . . don't wait."

New Officers for American Heart Association

Dr. Louis N. Katz, F.A.C.P., Director of Cardiovascular Research, Michael Reese Hospital, Chicago, became President of the American Heart Association for 1951–52, during the annual meeting of the Association in Atlantic City, June 6–10. At the same time, Dr. Irving S. Wright, F.A.C.P., College Governor for Eastern New York and Professor of Clinical Medicine, Cornell University Medical College, was chosen President-Elect for the 1952–53 term. Dr. Robert L. King, F.A.C.P., Seattle, Wash., was one of the five Vice-Presidents elected.

The Gold Heart Awards of the American Heart Association were presented by Dr. Katz to three physicians who have made outstanding contributions in cardiovascular medicine or to the Association. The recipients were Dr. James B. Herrick, M.A.C.P., Chicago, Ill., a Past President of the American Heart Association; Dr. Frank N. Wilson, F.A.C.P., Ann Arbor, Mich., and Dr. H. M. Marvin, New Haven, Conn.

New A.C.P. Appointments on the American Board of Internal Medicine

Dr. Thomas M. Durant, F.A.C.P., Professor of Clinical Medicine, Temple University School of Medicine, Philadelphia, and Dr. John Minor, F.A.C.P., College Governor for the District of Columbia, Washington, have been appointed by the American College of Physicians as members of the American Board of Internal Medicine for terms of three years, 1951–1954, to fill the expiring terms of Dr. Truman G. Schnabel, F.A.C.P., Philadelphia, and Dr. Alex. M. Burgess, Sr., F.A.C.P., Providence. Drs. Durant and Minor assume their duties as of July 1, 1951.

Cincinnati Society of Internal Medicine Organized

The Cincinnati Society of Internal Medicine was organized May 18, 1951, for the advancement of science in medicine, with special reference to internal medicine. An Executive Committee includes Dr. Joseph N. Ganim, F.A.C.P., President; Dr. W. Orville Ramey, F.A.C.P., Vice President; Dr. George X. Schwemlein, F.A.C.P., Secretary-Treasurer; Dr. Marion A. Blankenhorn, F.A.C.P., Dr. Harold K. Moss (Associate), and Dr. Robert M. Woolford (Associate). It is planned to hold regular monthly meetings, including scientific programs.

The new Health Center at the Ohio State University was dedicated to its role of teaching, research, and healing, at outdoor ceremonies May 15, 1951. Officials of the

university and state welfare and health departments participated in the ceremonies, and Dr. Raymond B. Allen, F.A.C.P., President of the University of Washington at Seattle, delivered the dedication address. The other speakers on the program were: Dr. Howard L. Bevis, President of Ohio State University; Dr. Charles A. Doan, F.A.C.P., Dean of the Ohio State University College of Medicine; Dr. John D. Porterfield of the Ohio State Health Department, and Judge John H. Lamneck for the State Welfare Department. Four buildings in the $15,500,000.00 center were dedicated. These are the 11-story, 600-bed University Hospital, the Dentistry Building, the Ohio Tuberculosis Hospital, under the State Health Department, and the Columbus Receiving Hospital, under the State Welfare Department.

Major General George E. Armstrong Becomes Surgeon General of the Army

Major General George E. Armstrong, for the past four years Deputy Surgeon General, was appointed Surgeon General of the Army for a statutory four year term, beginning June 1, 1951, succeeding Major General Raymond W. Bliss, F.A.C.P.

General Armstrong was born on August 4, 1900, near Springville, Ind. He received his A.B. degree in 1922 and his M.D. degree in 1925 from the University of Indiana. He served in the SATC in 1918, then enlisted as a private in the National Guard of Indiana in March, 1923, and was honorably discharged as a Technical Sergeant in 1925 to accept a commission as First Lieutenant in the Army Reserve Corps. Following internship at the Letterman General Hospital, San Francisco, Calif., he was commissioned a First Lieutenant in the Regular Army Medical Corps on July 9, 1926.

He attended the Medical Field Service School, Carlisle Barracks, Pa., and graduated with honors. Subsequently he attended the Army Medical School, Washington, D. C., the Advanced Course at the Medical Field Service School and the Command and General Staff School, Fort Leavenworth, Kans.

Thereafter he served at various posts, including the Walter Reed General Hospital, Washington, D. C., Fort Benning, Ga., Tientsin, China, Fort Stotsenberg, P. I.

During World War II, he served as Assistant Theater Surgeon, China-Burma-India, 1943–44, followed by two years as Surgeon of the China Theater. He returned to the United States in July, 1946, after three years of overseas service, to serve as Chief of Personnel, Surgeon General's Office, Washington, D. C. In June, 1947, he was appointed Deputy Surgeon General.

His decorations include the Legion of Merit, the Army Commendation Ribbon, World War I Victory Medal, the American Defense Service Medal, the Asiatic-Pacific Campaign Medal with three bronze stars, World War II Victory Ribbon, Chinese Cloud and Banner, Chinese Legion of Honor and the Order of the Crown of Italy.

General Armstrong, by provisions of the By-Laws, will automatically become the Governor of the American College of Physicians, representing the Medical Corps of the Army, and all proposals for membership from that Service will be subject to his final endorsement.

Major General Raymond W. Bliss Cited at Retirement Ceremony

After almost 40 years of continuous Army Medical Service, climaxed by the last four years as Surgeon General, Major General Raymond W. Bliss, F.A.C.P., was presented with the following testimonial by the Secretary of the Army, Frank Pace, Jr., at ceremonies held in the Pentagon, May 31, 1951:

"To this Testimonial, evidencing the esteem in which you are held in your splendid achievements, we affix our signatures with a sense of genuine gratitude.

"Doctor of Medicine, Surgeon and Soldier, yours is a record of outstanding accomplishment in the advancement of the health and welfare of the military service, the nation, and indeed all humanity. Your honorable and distinguished career has added luster alike to the annals of the medical profession and of the profession of arms.

"We salute you, and wish you Godspeed in the names of men, women and children of the Army who owe you so much."

Buffalo's Municipal Pound Ordinance

Buffalo, with the passage on April 30, 1951, of a municipal pound ordinance which provides that stray impounded animals may be turned over to approved medical laboratories for research, became the first city in New York State to effect such legislation.

Thirty-one other cities of the country have enacted similar measures, and four states—Minnesota, Wisconsin, South Dakota and Oklahoma—have state laws providing that unclaimed impounded animals may be turned over to medical institutions. Illinois and Pennsylvania are now considering legislation on this matter.

Under the Buffalo ordinance, approved laboratories are now able to purchase dogs from the municipal pound for the license fee of two dollars. Cats may be procured from the pound without cost.

According to the National Society for Medical Research, Buffalo city officials state that the matter now becomes a closed issue as far as the City Council is concerned, and that local antivivisection groups which have fought the matter have no further recourse.

National Society for Medical Research Announces

With the signing of the bill, which denies public funds to humane societies refusing to turn over unclaimed animals to medical schools, by Governor Kohler, of Wisconsin, on June 6, a long and bitter controversy between medical schools and humane societies of that state has been effectively settled. The bill not only provides a penalty for humane societies which fail to comply with the law, as enacted in 1949, whereby unclaimed animals are turned over to medical institutions for research studies, but also provides that humane societies failing to comply with the law become immediately ineligible for any further public assistance or public funds from any county, city or village. Failure to comply with the law may also constitute grounds for revocation of the humane society's corporate charter or may result in court action to require compliance. School officials declare that the training of medical students was handicapped and research projects slowed down with the shortage of animals as acute as ever before the enactment of the law, because of the tactics of the humane associations.

"Without this positive action," Dr. A. J. Carlson, F.A.C.P., President of the National Society for Medical Research, stated "a very small minority of the population was thus denying to the majority the benefits that are and can be available through animal experimentation, and the people of Wisconsin were not getting their just due from the law."

Opponents of the bill had claimed that the state had absolutely no right to lay claim to animals belonging to a private group such as the humane society.

Dr. Wesley W. Spink, F.A.C.P., College Governor for Minnesota, and Professor of Medicine at the University of Minnesota Medical School, is spending the summer in Europe, first to give a lecture in London and then to make for the United Nations a health survey of France, Italy and Yugoslavia.

Among the speakers at the Section on Gastro-enterology and Proctology of the American Medical Association at its convention in Atlantic City on June 13, was Dr. Benjamin M. Bernstein, F.A.C.P., Brooklyn, N. Y. Dr. Bernstein's paper was entitled "Acidity—Is It Related to the Ulcer Syndrome?"

Benjamin L. Brock, M.D., F.A.C.P., heretofore Chief of the Tuberculosis Service of the Veterans Administration Hospital at Downey, Ill., has accepted an appointment as Medical Director of the Central Florida State Sanatorium, Orlando, Fla., effective July 1, 1951.

Dr. Hobart A. Reimann, F.A.C.P., Philadelphia, Pa., was awarded the Charles V. Chapin Medal by the City of Providence, and delivered the annual Chapin Oration before the Rhode Island Medical Society on May 9, 1951.

At the Annual Business Meeting of the American Psychosomatic Society, held April 28, 1951, Dr. Sydney G. Margolin, (Associate), New York, N. Y., was named President-Elect, and Dr. Walter Bauer, F.A.C.P., Boston, Mass., and Dr. Henry W. Brosin, F.A.C.P., Chicago, Ill., were elected to the Council.

The 17th Annual Meeting of the Post Graduate Medical Assembly of South Texas was held in Houston, July 23–25. Among the guest speakers were Dr. Thaddeus S. Danowski, F.A.C.P., Pittsburgh, Pa.; Dr. Garfield G. Duncan, F.A.C.P., Philadelphia, Pa.; and Dr. Cyrus C. Sturgis, F.A.C.P., Ann Arbor, Mich.

Dr. Roberto F. Escamilla, F.A.C.P., San Francisco, Calif., addressed the Hollywood Academy of Medicine on May 10, on the subject, "Pituitary Insufficiency."

A portrait of the late Dr. Roy R. Kracke, F.A.C.P., former Dean of The Medical College of Alabama, was presented to The Medical College at a ceremony held at the Jefferson-Hillman Auditorium in Birmingham on May 20.

ABSTRACT, MINUTES OF THE BOARD OF REGENTS, ST. LOUIS, MO., APRIL 10, 1951

The second meeting of the Board of Regents during the 32nd Annual Session of the American College of Physicians was held at Kiel Auditorium, St. Louis, Mo., at 12:30 p.m., Tuesday, April 10, 1951, with President William S. Middleton presiding and Mr. E. R. Loveland, acting as Secretary, with twenty-one Regents in attendance plus the Chairman of the Advisory Committee on Postgraduate Courses, Dr. Thomas M. McMillan.

A digest of the Minutes of the preceding meeting was read and approved.

Two articles of business from the previous meeting required attention:

1. After general discussion, a resolution was adopted providing that Fellows of the College be permitted to bring or to introduce guests who are bona fide Residents of their hospital staffs, to the Annual Sessions of the College without payment of a registration fee. Heretofore, only Residents of local hospitals, participating in the program, were admitted without a registration fee, this ruling having been a part of an attempt to keep the Annual Sessions of the College from growing so much that members themselves could not be accommodated at some program functions. It was felt, however, that bona fide Hospital Residents would not swell the attendance by more than 250 additional registrants.
2. The second item of referred business was the matter of the so-called Survey Report of Dr. Charles A. Doan, Chairman of the Board of Governors Committee. The Board of Regents decided at this time that action on the report would be more or less premature until the Board of Governors itself had come to some conclusion about the report and had made recommendations to the Board of Regents.

A report on a meeting of the Advisory Council on Medical Education held at Chicago, February 11, 1951, was received from Dr. M. A. Blankenhorn, official representative of the American College of Physicians. In accordance with observations of the activities and accomplishments of this Council, it was felt that the College accomplished nothing of value and a resolution was adopted whereby the College withdrew from representation on said Council.

Dr. George Morris Piersol, official representative of the College on the Council of Administrative Practice of the American Hospital Association, Committee on Purchasing, Simplification and Standardization, reported that that Committee had met twice with representatives of the American Hospital Association, manufacturers of thermometers, representatives of the Pure Food and Drug Administration of the Social Security Agency of the United States, and others. The Standardization Committee has paid the expenses and carried on in an earnest and sincere manner. Deliberations have concerned chiefly the technical side of making thermometers, best ways to sterilize thermometers and more specific information as to how long, for instance, a thermometer should be kept for oral temperature, how long for rectal temperature, etc. Doctor Piersol felt the work was worthwhile, even though it may not concern too much the College.

A communication in the form of a set of resolutions was received from Dr. Donald M. Willson, Sr., F.A.C.P., of Milwaukee, Wisconsin, dealing with extensive publicity in the lay press of unsubstantiated and often doubtful results of medical research, causing false hopes to be raised among relatives and friends of patients with serious illness. The Board of Regents considered it unnecessary to take formal action on the resolution

since the College is already on record, through its Constitution, By-Laws and Fellowship Pledge, as opposed to such publicity.

Dr. Thomas M. McMillan, Chairman of the Advisory Committee on Postgraduate Courses, reviewed in considerable detail the Postgraduate Program of the College during the past year. He stated, in part, that the Committee has been considering ways and means to uncover new course directors, men who are growing, developing and probably assuming a position where they are quite capable of becoming excellent directors of College courses. He referred to the exceedingly fine group of directors who have contributed so much to the Postgraduate Course Program, which has now grown to the point where 1,071 doctors were registered in the College courses of the past year. The Committee aims to schedule approximately 18 courses a year and, as usual, will check the success of each course by communicating with every registrant. He then presented the schedule of postgraduate courses recommended for the autumn of 1951 and outlined a list of courses in course of preparation for future semesters. His report was approved and the schedule of courses has already been published to the membership, as well as elsewhere in this journal.

Dr. George Morris Piersol, Chairman of the Committee on Technical Exhibits and Advertisements, stated that during the year the Committee has reviewed scores of products that have been submitted either for advertising or exhibit. Whenever a product has not been approved by the Council on Pharmacy and Chemistry of the American Medical Association, the Committee requires the unanimous acceptance by the members of the Committee before such product may be advertised in the Annals of Internal Medicine. The Committee has tried to keep the advertising on a proper level, and Doctor Piersol asked, on behalf of the Committee, that if any member of the Board of Regents knows of any product that has been accepted for advertising but which in his opinion is not suitable, the Committee will welcome any criticisms or suggestions. In regard to the Technical Exhibit he said, "Our Technical Exhibit at this Annual Session has been inspected by the entire Committee, supplemented by the help of others. We inspected every single exhibit and, as far as we can determine, there was nothing undignified or unethical about any of them. We have asked many for criticisms, and so far we have no exhibits subjected to any unfavorable remarks by the Fellows. Another point is that the exhibitors feel thoroughly pleased with the way our exhibit is managed. Many who have inspected the exhibit think it is an extremely broad and successful one on a high plane of ethical efficiency. Several Fellows of the College commented favorably and only yesterday one told us that he was very much surprised and gratified to find there are no booths giving out cigarettes, selling soft drinks and other irrelevant products."

Dr. William D. Stroud, Treasurer, made the following report:

"Mr. President, Masters and Fellows of the College: The detailed statements of operation of the College for 1950, along with the certified public accountant's report, will be published in an early issue of the ANNALS OF INTERNAL MEDICINE.

"During the year 1950 the College added to its General Fund $72,609.57; to its Endowment Funds, $26,633.78; total, $99,243.35.

"The gross assets of the College, as of December 31, 1950, amounted to $766,902.50, divided as follows:

General Fund	$412,298.25
Endowment Fund	333,833.42
James D. Bruce Fund	10,395.83
A. Blaine Brower Fund	10,375.00
	$766,902.50

"The College operated wholly within its budget. In fact, the income exceeded budgetary expectations, whereas expenditures did not exceed appropriations of a year earlier. The investments of the College are supervised by an investment counselor and by the Committee on Finance, and are carefully reviewed periodically. As of December 31, 1950, the College held Investments at Book Value totalling:

Endowment and Restricted Funds	$349,259.87
General Fund	266,485.35
	$615,745.22

and as of last November showed an appreciation of $48,887.00, and the average yield at that time was 4.58%.

"The Board of Regents has approved a budget for 1951 calling for an estimated income of $286,600.00 and an estimated expenditure of approximately $256,670.00, leaving an estimated balance of approximately $29,900.00.

"The financial policies of the College continue to be conservative at all times."

By resolution, the Treasurer's report was accepted.

Dr. A. B. Brower, Chairman of the Committee on Finance, presented the annual report which included the following:

1. A recommendation that the College revise its current level of salary classifications for full-time teachers or research workers, providing that instead of $5,000 being the demarcation point, that $7,500 be substituted, thus providing that full-time teachers and full-time research workers, in institutions not subject to profit, shall have a reduction in their initiation fee and annual dues to $50.00 and $12.00, respectively, if their annual salaries are $7,500 or more, and that those with salaries of less than $7,500 shall have a reduction in these fees to $25.00 and $12.00, respectively. (This recommendation was approved by resolution of the Regents.)
2. All accounts of the College are audited by a certified public accountant.
3. The College funds increased as follows during the year 1950:

	Balance Jan. 1, 1950	*Balance Dec. 31, 1950*	*Increase*
General Fund	$339,668.68	$412,298.25	$ 72,629.57
Endowment Fund	307,199.64	333,833.42	26,633.78
Brower Fund	7,500.00	10,375.00	2,875.00
Bruce Fund	10,395.83	10,395.83	
	$664,764.15	$766,902.50	$102,138.35

4. The gross assets of the College as of December 31, 1950, amounted to $766,902.50.
5. Comparative total income and total expenses for the General Fund were as follows:

	1949	*1950*
Total Income	$236,649.40	$298,982.55
Total Expenses	174,514.11	205,649.61
	$ 62,135.29	$ 93,332.94

6. The average annual yield on invested funds was 4.66%.
7. At current market value, as of March 20, 1951, the College portfolio showed an appreciation of $79,590.50.

Doctor Brower proceeded to give a report of all security transactions since the last meeting of the Board of Regents and presented recommendations for further purchases and sales of securities; the recommendations being approved by the Regents by formal resolution.

The Finance Committee suggested that a study be made of the proportion of bonds and common stocks in the General Fund by Drexel and Company, and also by three other sources with a view to determining the advisability of continuing present investment policies.

The report of the Finance Committee was, by resolution, adopted.

Dr. LeRoy H. Sloan, Chairman, presented the report of the Committee on Public Relations, which included among other matters the following:

1. The approval of bills in various state legislatures providing for the use of pound animals for supervised research in accepted institutions.
2. The acknowledgment of a communication from a New York Law Firm relative to a report of the Special Committee on Retirement Benefits for Lawyers, drawing to the attention of doctors a resolution seeking legislation which would provide for retirement income of lawyers who are in much the same category as other professional men, including doctors.
3. The Committee approved in principle a communication from Dr. A. H. Aaron, F.A.C.P., relative to the junior candidate plan of another medical group which provides supervision and guidance in postgraduate training.
4. The recommendation of approval of the waiver of annual dues of two Fellows of the College who are now completely incapacitated and out of practice.
5. The acceptance of the resignations of 40 Associates and 1 Fellow, the resignations of the Associates being almost wholly due to the fact that they had not been able to fulfill the requirements for advancement to Fellowship within the maximal period of five years and who preferred to be recorded as "resigned" rather than "dropped." Most of these Associates had failed to attain certification in their specialty boards.
6. The recommendation that 1 Fellow and 3 Associates who were delinquent in dues for two or more years be dropped, in accordance with provisions of the By-Laws.
7. The recommendation that the College bear one-fourth the expenses (a legal bill of $700.00) for the setting up of the charter and by-laws of the Joint Commission on Accreditation of Hospitals.
8. A recommendation that letters be sent to the respective Surgeons General of the Armed Forces and the Medical Director of the Veterans Administration, thanking them for delegating their duties as College Governors at the St. Louis Annual Session to such interested and high-ranking internists as those who were selected for this annual meeting of the Board of Governors.

The recommendations of the Committee on Public Relations above presented were, by individual resolutions, approved.

On behalf of the Committee on Public Relations, Doctor Sloan then took up the question of the Joint Commission on Accreditation of Hospitals which is a proposed cooperative plan of conducting the entire hospital inspection and accreditation plan among the American College of Physicians, American College of Surgeons, American Medical Association and the American Hospital Association, with the possible later addition of the Canadian Medical Association. Doctor Sloan distributed copies of the proposed Charter, Constitution and By-Laws and discussed in detail the provisions of the proposal. The matter was discussed at great length and the following recommendation was, by resolution, approved:

"The College approves entering upon the plan for a two-year trial period and approves a budget of approximately $16,000 for the first year and $12,000 for the second year."

The appointment of commissioners and a member of the Advisory Committee, representing the American College of Physicians, was deferred pending adoption of the plan by the other interested medical groups.

Dr. Walter B. Martin, Chairman of the Committee on the ANNALS OF INTERNAL MEDICINE, reported progress on behalf of the Editor and referred particularly to the publication of a Part II Edition of the Annals which will be devoted wholly to the publication of a monograph on "The Acute Irradiation Syndrome," the cost of which will be borne in full by the Atomic Energy Commission. The Atomic Energy Commission has selected as first choice the ANNALS OF INTERNAL MEDICINE for the publication of this material, and the Editor is scheduling it for the early autumn.

President Middleton reported that there had come to his attention informally the desire of the Royal College of Physicians and Surgeons of Canada for an official interchange with our College at the time of the Annual Session. He recommended that the succeeding President of the College may wish to give this suggestion a thought for the coming year.

President Middleton appointed Dr. Cyrus C. Sturgis Secretary-General pro tem to perform certain duties regarding the signing of the Stengel Diploma for the current year.

Attest: E. R. LOVELAND,
Secretary, Board of Regents

ABSTRACT, MINUTES OF THE BOARD OF GOVERNORS, ST. LOUIS, MO., APRIL 11, 1951

The second meeting of the Board of Governors was held during the 32nd Annual Session of the American College of Physicians at St. Louis, Mo., at 12:30 p.m., April 11, 1951, with Dr. Walter L. Palmer presiding, as Chairman; Mr. E. R. Loveland, acting as Secretary and with 61 Governors or their alternates in attendance, and with President William S. Middleton and President-Elect Maurice C. Pincoffs present as guests.

After the recording of the roll, the Secretary reviewed the Minutes of the preceding meeting of the Board which stood approved as read.

Chairman Palmer announced that there would be an indoctrination meeting of incoming Governors and any others interested on Thursday afternoon, April 12, immediately following the afternoon General Session, the purpose being to instruct new Governors in respect to their duties and to acquaint them more intimately with the standards for membership in the College.

Chairman Palmer then reported to the Board of Governors various resolutions that had been adopted by the Board of Regents at its meeting the day previous.

President William S. Middleton and President-Elect Maurice C. Pincoffs addressed the Board of Governors briefly.

Dr. Thomas M. McMillan, Chairman of the Advisory Committee on Postgraduate Courses and College Governor for Eastern Pennsylvania, made a long and detailed report on the Postgraduate Course Program, past, present and future.

Dr. Robert Wilson, Jr., Governor for South Carolina, was unanimously re-elected for a term of three years to the Committee on Credentials.

Chairman Palmer called for an open discussion of the subject of Regional Meetings, a program that is carried on wholly by the Governors of the College.

The Secretary read a letter from the Governor for Tennessee, Dr. William C. Chaney, concerning the Mid-South Regional Meeting held at Memphis, during the past winter.

DR. WILLIAM C. CHANEY: "Mr. Chairman, Governors: I want to mention a few other points. After I wrote that letter, I had a meeting with Doctors Carter and Findley, Governors for Texas and Louisiana, respectively, to discuss things that we should have done at our Regional Meeting that would have contributed to its further success. We planned to have four hundred doctors in attendance, but had only one hundred and ninety-six. The meeting was quite successful, because of the program. Had we adhered to the points I am going to give, I believe we would have had the larger registration.

"One should begin working on a meeting a year in advance by writing personal letters to the members of the College in the territory covered, asking members to suggest subjects and asking for their choice of the time of year for the meeting. We plan to have a Mid-South Regional Meeting once a year, and to have it about the same time each year.

"Programs should be prepared for publication early and sent adequately in advance. We prefer a two-day program, consisting of an afternoon, evening and the next morning.

"We recommend, where available, consultation with the medical schools in the States covered, in order to obtain suggestions for subjects and speakers. In our case, we consulted the ten medical schools in our district, asking each to furnish three subjects, thirty in all. From these thirty, we selected fourteen, in order to have a well rounded program.

"Go the limit on publicity. Procure pictures of the guest of honor; make releases to medical journals and publications in the area and to newspapers, making it plain that the meeting is open to all physicians interested in Internal Medicine, and that the meetings are not restricted wholly to the College. In the mid-south most physicians will travel three to four hundred miles to attend an excellent meeting. We had a program so good that any one would go four hundred miles to hear it. Let the doctors know about it before the meeting, and not afterwards. Select for the meeting a city with good hotels and places of interest, so the physician's wife will come also. Have an information bureau in the headquarters hotel for the visiting women. Have a fine banquet one evening for the physicians and their wives, and make it different. Start building up enthusiasm for the meeting a year ahead and keep this going. Get your meeting at the top of the busy doctor's 'must list'." (Applause.)

CHAIRMAN PALMER: "Thank you, Dr. Chaney. Dr. Menninger, our Governor for Kansas, has some unusual ideas about Regional Meetings, and probably you all know about the newsletter which he sends out to the members in his district periodically. I should like him to tell you about his ideas, and particularly about the summaries of the program which he sends to the members in his state."

DR. WILLIAM C. MENNINGER: "We have felt that it is worth while to make every one in the state feel he really belongs. To do that was a matter of communications over the year, about every two months through various sources, including the Central Office of the College. I can get some kind of news and talk about the next meeting date and the program. At the time of the meeting, we ask each speaker to hand in a brief abstract of his paper, so that we may distribute a summary of the program to every member who was prevented from attending; included also is a report on whatever business was transacted at the meeting."

CHAIRMAN PALMER: "I am sure the men appreciate receiving summaries of the papers. I have been very much impressed with the success of that maneuver. All

the men who attend our Postgraduate Courses also want to take home with them resumes of the papers presented at the course. I am sure the idea of the summaries met with great enthusiasm and appreciation by those present, as well as those who were absent."

DR. JOHN MINOR: "I want to ask Dr. Menninger how he finances this newsletter."

DR. MENNINGER: "It is a very, very minor cost—a matter of mimeographing and sending the letter to about seventy-five or one hundred physicians. It wouldn't break any one's pocket book, but our Fellows have been very gracious in setting up a 'chairman's fund'—every one contributes as he wishes, and nobody is dunned."

MR. LOVELAND: "I want to remind the Governors that whenever they desire to send out letters, notices or announcements, they may call upon the Central Office for the duplication and mailing of the same."

CHAIRMAN PALMER: "Two of the Governors attended a meeting of the Committee on Credentials on April 7, to obtain a sort of indoctrination in the problems of fulfilling requirements of candidates for membership. We should like to hear from Dr. Paul H. Revercomb, Governor for West Virginia, and Dr. Charles H. Drenckhahn, Governor for Southern Illinois."

DR. PAUL H. REVERCOMB: "I spent most of Saturday at the session of the Committee on Credentials. It was an enlightening experience to me. I had no previous idea this Committee had such a big job. Attendance at this meeting is the best form of indoctrination that I can think of."

DR. CHARLES H. DRENCKHAHN: "I was much impressed with the meeting, and I can assure you that any new Governor that can attend will know the problems of the Committee and will benefit by attending one of their meetings. I was also much impressed with the seriousness of the problems and the excellence of the management. I was also impressed, after attending the meeting, that there is a need for modifying our rules, such as may come up from Dr. Doan's survey."

DR. WOLVERTON: "I wish to make again the suggestion that the proposal form should be furnished in duplicate, so that the Governor may retain one copy for his file and thereby have a record of the case until the candidate has qualified for election."

MR. LOVELAND: "It would be perfectly possible to reprint the proposal form and draw it up in duplicate, with one copy marked for retention by the Governor. It would also be possible to ask the sponsors to submit their letters in duplicate, one copy of each to be retained by the Governor."

DR. MINOR: "Mr. Chairman, I move that the proposal form for membership be prepared in duplicate, and that the covering letters from the sponsors shall likewise be required in duplicate, the duplicate copies to be retained by the respective Governors."

The motion was seconded by Dr. W. C. Menninger and unanimously carried.

CHAIRMAN PALMER: "We shall now ask Dr. Charles A. Doan to bring to the floor for discussion the report of his Survey Committee. In so doing, the Chair would like to remark, as others have already, that this proposal seems to be a most important one. As I see it, the problem, as outlined by Dr. Doan's Committee, is that of inclusion on the one hand, or exclusion on the other. The question has been raised, Dr. Doan, as to how much this plan would increase the size of the College? May I ask you to speak on that point, and anything else that you wish to discuss in connection with the proposal?"

DR. CHARLES A. DOAN: "Mr. Chairman and Governors: It seems to me that the results of the proposal of your interim Committee in terms of the size of the College would remain with those designated to have that responsibility, namely, the Committee on Credentials.

"The recommendation that certification by the American Board of Internal Medicine be a prerequisite for Associateship instead of for Fellowship, as at present, carries with it no implication, unless you wish to make that the sole criterion for admission to Associateship. Your Committee did not mean to imply that. The implication was that a number of Fellows have expressed to us their feeling that further higher hurdles than are set up by our representatives on the American Board of Internal Medicine for certification would be too bad; that these men are working hard on the basic credentials that will be necessary to enable them to be accepted and recognized as internists, and that, therefore, subject to their acceptance, personally and otherwise, by Fellows in their vicinity, after having passed their board examinations, after having attended some of our scientific programs, including Postgraduate Courses, we then should think long before we exclude them on a still different basis, either with regard to the size of the College or any other consideration, other than ethics, ability, personality, etc. It would not change the fact that the Committee on Credentials and the Governors in recommending candidates to the Credentials Committee would still have the same prerogatives that now exist.

"With reference to how much larger this College might become under these circumstances, it would be conditioned somewhat upon the number of men that are certified by the American Board of Internal Medicine in the future and the decision of the Committee on Credentials relative to individual merit for election to the College, unless there is a limit placed upon the total number of men whom this College will accept under any condition. That, so far as I know, has not been a matter of legislation by the Board of Regents. Since our meeting on Sunday, members of our Committee have conferred with several of you and met together this morning to pool the information we have obtained with reference to their reaction to this general attempt to redefine our position with reference to a growing country, with a growing knowledge of medicine and with an increasing number of intelligent men to put into practice these things that are coming.

"We would like to present three summarizations for your consideration this afternoon, which to the best of our knowledge would crystallize as much as it would be possible to consider at this time. I would like, therefore, Mr. Chairman, to present this summarization, which I think comes before the Board of Governors with the thought in mind if it is approved to pass it on to the Board of Regents as our considered judgment in terms of the unanimity or lack of unanimity with which these three items may be received by you today. This is a supplemental addendum to the report made on Sunday.

"This Committee recommends for consideration of the Board of Governors:

(1) Certification by the American Board of Internal Medicine, or by the certifying board in an allied specialty, as a prerequisite for election to Associateship in the College;
(2) There shall be no limit to the term of Associate membership, except under circumstances of grave professional or personal misconduct;
(3) Associates of the College prior to consideration for election to Fellowship shall (a) have been Associates for at least three years and (b) show evidence of progressive professional attainment and advancement."

CHAIRMAN PALMER: "Thank you, Dr. Doan. Dr. Wilson, as a member of the Committee, will you comment on this report?"

DR. WILSON: "Mr. Chairman, Gentlemen: Briefly speaking on one or two of these points, first, the requirement for certification before election to Associateship, I should say, of course, this is a matter for the Regents to decide eventually, but it might well be certification or presentation of evidence that the candidate is an adequate internist. Now, certification should cover the professional qualifications and on that point speak

for itself. I think it would be a good idea and I think in general, in accordance with what we said today, it is desirable to make it a little more difficult for a man to become an Associate, and thus not be in a position where we would have to drop him for membership in the society. If we had more Associates and fewer Fellows, it might create other problems. We want to go further than selecting just 'good doctors'; we want to select the man who has adequate evidence that he is a professionally trained, experienced and adequate internist. I think we could also insist on having a man get established in his community for a longer period of time before he is eligible for election to Associateship, in order that his colleagues may know what kind of a man and doctor he is, whether he works well with other men, whether he is of good moral character, and all of those things.

"As to the second point in the recommendation, with regard to having no time limit on Associates, I would be inclined to go along with that, too. Certainly, I would favor increasing the maximal period of Associateship beyond five years, which is the limit at present. We might first make it ten years, but I think eventually we are going to have to make it an indefinite period.

"As to the third point, the presentation by the candidate of evidence that he has advanced in professional standing and has shown proof of attainment, could well be required before election to Fellowship. One of the criticisms we have had is that a candidate is so busy taking his board examinations that he hasn't had time to progress in hospital appointments, to write anything, etc., but if we require certification before Associateship, that would no longer be a justifiable excuse for failure to show advancement. I think those two things go along together very well.

"I do not think the Central Office need notify an Associate that he is now eligible to present his credentials for Fellowship. I think the initiative should come either from the candidate himself or from some Fellow in his community. In other words, we should not press the candidate into presenting his credentials for Fellowship, but let the initiative come from him or his sponsor.

"I have talked to many members of this group concerning the written theses or the publications that have been required. Frankly, I do not know the answer. I believe like Dr. McGee that it is a good exercise to require something in writing. Several candidates have spoken to me during the last few days concerning the presentation or the preparation of a thesis of ten thousand words. As a member of the Credentials Committee, I haven't ever counted the words in any of the theses submitted for review, but I doubt if I have ever had one that large. I told the candidates there is a differentiation in the action of the Credentials Committee between the candidate who is out of medical school, who lives in a big center and the candidate who lives in the small community. If the latter candidate addresses his staff meetings, it is possible for him to send copies of those presentations, for if we know his situation is such that he can't do any really scientific work, we can take a more lenient attitude toward contributions, but take into consideration his other activities."

CHAIRMAN PALMER: "Thank you, Dr. Wilson. Will the other member of the Committee, Dr. Wilbur, comment?"

DR. DWIGHT L. WILBUR: "Mr. Chairman, members of the Board: I have little to add. I believe the report, as Dr. Doan read it, speaks for itself. There is no intent on the part of the Committee to write into its report all of those details that would be required of an individual prior to election to Associateship or Fellowship in the College, but it does expressly recommend those things which have been mentioned."

DR. WARD DARLEY: "My first remarks may seem a little removed from the Committee's report, but they are stimulated not only by that report, but by the very excellent discussion we heard Sunday evening regarding some of the general problems facing the specialty of Internal Medicine. You will recall Dr. Palmer gave us some very interesting figures, and with your permission I would like to add some other

information which I think pertinent. These figures will appear in the next issue of the publication of the Association of American Medical Colleges. These figures are taken from the last two editions of the Directory of the American Medical Association and apply only to physicians in active practice, not physicians who are not in active practice. The number of physicians in this eleven-year period increased by 19%; the number of specialists during the same period increased by 98%; the number of general practitioners decreased by 13%.

"Now, my question is, is this a good thing? I think too much of anything is not a good thing, and we may well be approaching the time when we are going to have to deal with the problem of too many specialists in this country. The report to which I refer will also include the result of correspondence with all of the specialty boards for the years 1948 and 1949 as to their examination experience. All of the boards were very co-operative, and I think it significant that with the exception of the Board of Otolaryngology, which fails an average of about 60% of its candidates, and another board which fails an average of 12% of its candidates, all the other boards, which have a Part I and a Part II examination, are consistently failing between 30% and 35% of its candidates for certification.

"I realize many candidates who fail an examination take it again, and many of them are eventually certified, so it is not safe to say that a third of all individuals seeking certification fail in their objective. I think it is safe to say that a very significant number do fail, and I do not think it takes any stretch of one's imagination to realize what a waste of effort is represented in such a high percentage of failures. Now then, in 1949 there were 18,669 individuals taking graduate training over the country. That is a significant figure. It seems to those of us who are interested in medical education in general that something radical may be wrong with graduate training in medicine in this country. Does the high percentage of failures represent poor selection of graduate students? Poor training of graduate students? Inadequate examination of the graduate students? Or a combination of all three? Most of the examining boards should have the necessary information in their records now to come forth with some very valuable studies. It would be most helpful if we knew the training background; if we could see an analysis of the training background and a comparison between those who succeed in certification and those who fail. It would be worth while to see some study made of the various training methods; an analysis of the type of training that the successes and the failures are receiving, and a consideration might be given by many of the boards to an improvement in the methods of examination; more consideration might be given to an estimate of motivation behind the student seeking certification. It would also be interesting to see what happens to the individuals who do not become certified; do they continue in specialty practice, and thus are they thwarting the chief objectives of the boards to inject some semblance of control into specialty practice?

"It is my feeling, and I think it is shared by many others, that we are headed for difficulties in the training and the practice of specialism. I think it is realized by all that the best leadership is that which is based upon the anticipation of difficulty and a setting in motion of measures aimed at correcting difficulties before crises develop. I think the American College of Physicians is really standing out as one organization of medical men in the country that is providing very positive information, exhibiting leadership, and I would like to suggest two things that this College might do that would anticipate problems that are in the making. One of these is that the medical schools of the country be encouraged to set up graduate schools of clinical medicine, and that candidates for the specialty of Internal Medicine be encouraged to seek training in such institutions. This would mean automatically that the candidates for training would be more carefully selected; it would mean that the training programs would be of the best; it might mean that an education might be the objective of the training

program, rather than a certificate, which I think today is all too often the case. We would see a lowering of the failure rate. We might eventually see fewer specialists trained.

"My second suggestion is that the training program of the internist be broadened, so that as a result the service activity of the internist would be broadened. It is the feeling of many of us that this trend toward specialization is segmenting the craftsmanship of medicine to a dangerous extent. It means the segmentation of the patient. Fewer and fewer doctors are interested in the continuing care of the ambulatory patient and all that that implies. Too many have been interested in the analysis and the evaluation of the complicated problem involving pathology. I think there is a distinct need in this country for the family physician who is a general manager type of family doctor. I doubt if the general practitioner is going to rise to the occasion. Dr. Palmer and I have discussed this many times over the years, and in the past my feeling has been that the general practitioner, through the newly formed American Academy of General Practice, might encourage this type of practice. I am becoming rather discouraged in that viewpoint and beginning to swing to Dr. Palmer's viewpoint that it should be the internist who assumes this rôle in American medicine.

"Now, by broadening the base of the training of the practicing internist, in the position of practicing pediatrics, practicing psychiatry, in addition to practicing internal medicine as we know it, with a strong flavor of preventive medicine injected into the whole thing, and I think this College can encourage medical schools to train internists from this viewpoint, we may be contributing to something that would in itself tend to correct any imbalance we may be approaching, insofar as the number of specialists and general practitioners is concerned.

"I think this report of Dr. Doan's Committee is right down the alley of this type of thing. I know the American Board of Internal Medicine is prepared to waiver, because that board does not now frown upon training in pediatrics, or in psychiatry, as part of the preparation. With a little encouragement, the American College of Physicians may very well play an important part in this type of development. Associates could be the practitioners of the practitioners group and Fellows can be picked from those who are interested in teaching and in investigation and becoming consultants. We would be doing something that consequently would mean encouragement to the younger man and stimulation to the older man to keep the avenue for continuing education and improvement open at both ends, and I am extremely interested in this report and strongly in favor of it." (Applause)

Dr. Harry T. French: "Along with the figures Dr. Darley has presented, it seems to me that the comparison between residents and internes is important. I understand the ratio between internes and hospital residents in 1940, as compared with the present, is an inverse one. In 1940 we had about twice as many internes as we had residents; in 1950 we had twice as many residents in training as internes. If that is so, it seems to me that in spite of the greatly increasing percentage of diplomates of the board, we are bound to get an increase in men who will pass, and if this recommendation that certification be made a prerequisite for Associateship goes through, that would practically mean that all of these would be eligible for Associateship and our number of Associates would be bound to increase. I would like to inquire of Dr. Palmer if he has any ideas as to whether this number of residents that are being trained is temporary, or whether it will continue in present numbers, whether it is a post-war development, or whether the number will still tend to increase?"

Chairman Palmer: "Dr. French, I do not know the answer to your question. During the last few years the number coming before the American Board of Internal Medicine has progressively increased. The Board has certified during the last two years between seven and eight hundred men each year. In a recent discussion with Dr. Pincoffs, I suggested that if all of these young doctors, after they complete their

internship, are required to go into military service as seems likely for period of one to three years, during which time they might acquire a wife and children, higher standards of living than they had in medical school or during internship, will they be willing to come back and go through residency programs as they have in the past, or will they be eager to get into the practice of medicine, make some money and maintain their standard of living and support their families? Dr. Pincoffs, perhaps you would like to speak on that."

DR. PINCOFFS: "I appreciate the opportunity to comment on this. As far as the point you brought up is concerned, I feel that there are self-corrective influences in the number of men who will go through the arduous training to become certified specialists and that eventually will affect the membership of the College. The one factor in that self-corrective mechanism is no doubt the one you brought up. Figures presented are naturally dependent on the very uncertain retention of the status quo in international affairs, but I am informed that if we maintain a force of about three to three and one-half million in our Armed Forces, something like this will happen. We are going through an adjustment period now and balance will be reached in about 1953. At that time the Armed Forces will require for replacements approximately four thousand physicians a year, and no doubt the majority of them will have had only one year of internship. However, at the same time the Armed Forces will release into civil life the same number, minus those who elect to remain in the regular service and minus those who have died or have been killed. But, roughly, there will be an exchange between the Armed Forces and that will mean that while we will lose out of say sixty-five hundred men who have completed an internship, two-thirds of them to the Armed Forces, there will be a potential returning to civilian life of slightly less. I estimate that the average age of those returning will be somewhere between twenty-eight and twenty-nine. They will have been receiving on the average of $4,500.00 to $5,000.00 a year, and it is reasonable to suppose a great many of them will be married, and I do not believe we shall have as many applicants for assistant residencies out of the group as if we had taken that number of men at the end of their internships, offered them the position then and there. They will be older, responsibility will be greater, and they will have grown accustomed to a scale of living beyond $50.00 or $75.00 a month offered in most cases to assistant residents.

"I would like to comment on another point about the program submitted by Dr. Doan's Committee, and that is the difficult question, if we have permanent Associates, of determining who out of those Associates should be raised to Fellows. It is my present conviction, open to change and there may be many other points of view brought forward by the Regents, that it is impossible to do that adequately on the basis of the man presenting his claim to be elevated to Fellowship, and the decision being made remotely by a Credentials Committee.

"It was suggested in the report that the Credentials Committee would review the several thousand Associates all over the country every year and select those to be raised to Fellows. I cannot conceive that any Committee can do that wisely. I would like to propose, for your consideration, a different method, and that is to place on the Governors an added responsibility, that with their Committee, and I think a Committee would be entirely necessary, to review annually the Associates within their individual regions, and our Credentials Committee to then consider those selected. I feel strongly against laying too much stress on papers or theses, not that they might not bear a weight, but I think other things should be considered, if we are going to make Fellowship increasingly selective. It can be done gradually over a long term of years, so that it eventually will have even more distinction than we dream of today.

"I would feel that men should be selected possibly through three main channels, or by consideration of three main attributes. In one I will place research and teach-

ing, prominence in those fields. In the other, I would place the man's standing as a physician in his community, and I mean by that, does the Governor and the Credentials Committee feel that this man stands out as someone who is entitled to recognition? One tangible item of that is that the average young certified physician doesn't do consultant work. He does very little in a big medical center, but a great deal more in a small community. It is when he stands out as a consultant internist that he should be recognized, I think.

"Thirdly, how far has that individual gone to bear his share of the load of the medical profession or organization in the hospital? Is he a selfish fellow who does nothing but practice, does nothing in his medical society, nothing in the hospital, nothing to stand behind the public health movements in his community? I would consider that very much against his election to Fellowship. On the other hand, if in addition to being an excellent internist, he stands out as a medical citizen, I think that should be given great weight in honoring him with Fellowship. To summarize that conception, election to Fellowship would be through nomination by his peers, after they reviewed his Associateship years, bearing in mind those three types of qualifications. To the Credentials Committee I would leave the final power of approving or disapproving. In that way we would have a more democratic and very sound way of passing this honor of Fellowship on to the selected men from this permanent body of Associates." (Applause)

CHAIRMAN PALMER: "Thank you very much, Dr. Pincoffs. Dr. Kinsman, would you like to comment?"

DR. J. MURRAY KINSMAN: "First, I am speaking partly as a member of the Credentials Committee, and, secondly, as an interested Governor. I think Dr. Doan and his Committee have done a good job here, and I go along all the way with them in principle. Dr. Pincoffs has expressed my thoughts. The Fellows from Kentucky raised a very serious objection to using writings and publications as a major criterion for advancement to Fellowship. Dr. Wilson referred to that a moment ago, and we have had some merry disagreements in our Credentials Committee concerning that point. I was glad to hear Dr. Pincoffs' opinions, because I, too, feel strongly that we should not require writings on the part of candidates as a major criterion. There may be times that we have to, but where a candidate is well known to his Fellows, it seems to me that nothing can take the place of that in evaluating his credentials. If we place the job on the Governors of selecting each year possible candidates for advancement to Fellowship, that will require further indoctrination of the Governors. I believe that a continuing interest in the College of Physicians, as shown by attendance at annual meetings and other sessions and activities, is a very important part of the whole picture. A candidate who has not displayed a continuing active interest in the College and in Internal Medicine should not be elected to Fellowship."

DR. FULLER B. BAILEY: "I feel Dr. Doan and his Committee have thought this matter through very thoroughly. I have a few problems, but they are only the problems that all of you have experienced. Unfortunately, one of the leaders among young men in my community was rejected for advancement to Fellowship, and that has had a deterrent effect on the older men in that community. Now, I am sure this rejection was mainly due to his not having made any contributions, and now two or three other young men have refused to have their candidacies go through, for they are fearful of being made targets, because if this one candidate was not accepted, they cannot hope to fare any better. I wonder if we continue the old program how high we could set our standards. Having passed their boards, these young men have acquired one thing they set out to do, and, of course, if they have not attended meetings of the College and shown continuing progress, they have nothing to stand on, but I wonder if we set the standards too high, if we will not lose many worth while young men we would like to have in the College. I feel Dr. Doan's Committee has

made a very definite contribution, and I certainly approve of what Dr. Pincoffs has said."

Dr. Ralph A. Kinsella: "There seems to me to still be unanswered one point. I can see the evidence of stiffening the requirements for admission to Associateship, but the point remains is what will happen to the man who deteriorates during this indefinite Associate term. What mechanism could be set up for retiring Associates from the College if it is evidenced that they are deteriorating in their communities? Would we want to be saddled with a certain number of such men for life?"

Dr. E. Dice Lineberry: "One time we are trying to cut down the College membership and the next time we are trying to increase it. Certainly, if we are going to let Associates remain for an indefinite period of time, without any means of letting out the undesirables, or the ones who cannot qualify for Fellowship, we will have increased our membership. If we are going to be an honor society, that is one thing. If we are going to continue our program of education for all, that is another thing, and I personally feel our Associateship to the present time has had a place. Perhaps we have been a bit lax in electing some Associates before they have attained a certain degree of prominence, but I think there are a very few men now being elected to Associateship who have not at least met the rquirements of the American Board. Mr. Loveland tells me that slightly over fifty per cent are now fully certified before election to Associateship."

Dr. Wolverton: "I hope we do not take any definite action on this question today, because the report needs reading and re-reading, and there will be more and more points to come up that enter into the final decision. You may remember in the report it states that all of Internal Medicine should, as far as possible, be represented within the Associateship of this College, and that there should be no large segment of internists outside the College, for obvious reasons. What is going to happen as the years go on to that group of men who fail to attain certification or membership in the College and who most likely will continue to practice Internal Medicine? It doesn't seem likely to me that a man who has spent three or four years on a medical residency is going into general practice just because he is not certified. Therefore, in time there will be a goodly number of men who have served medical residencies who have failed the Board who are going to practice Internal Medicine, and yet because they have never been certified, they could not become Associates of the College, assuming that certification becomes a prerequisite for Associateship. Perhaps those men are square pegs in round holes and may not actually become good internists, but the Board of Internal Medicine recognizes that its methods and selections are not perfect, and it seems to me quite possible a good many of those men may eventually become very good internists, and if the certification is an absolute prerequisite for Associateship they can never find a place in the College. Perhaps some provision should be made for such men. It seems to me that in addition to training, the mere acquisition of knowledge, it takes a particular kind of mind to make a good internist; he has to have certain native qualifications, with which he was born, to become a professionally successful internist, and it may well be that in spite of having those endowments, for the reason of lack of good training, he may have failed to attain certification. What will become of him?

Dr. Doan: "In a preamble to our original report, we recognize the reasons for and the presence of a variety of opinions among internists and among members of this Board and the Board of Regents on a subject of this kind, and this has been brought out by these various comments. During the past six or eight years there have been repeated discussions and more or less formal reports from time to time to make some change in the general plan of the College. Those have not succeeded in achieving a sufficient majority of opinion to become a policy of the College. I do not know the answer to some of the questions. I do think these three specific recommendations

that have been made do have certain relationships, one to the other, although they could be considered separately, but as a matter of bringing this situation to a focal point, I should like to state that our Committee felt that if a delay of a year or so were suggested, that each Governor be asked to consider this report after going home and then send back a written specific comment or recommendation, or criticism, for further consideration in adopting policies that the College might follow—that could readily be done and could be done within a brief period of time. However, to bring this particular consideration to a point which I think this group could either accept or reject, I will move that the supplemental report presented today of these three points be approved by this Board of Governors and referred to the Regents for their further consideration."

The motion was seconded by Dr. Leslie R. Kober, put to vote and carried.

CHAIRMAN PALMER: "With that, we discharge the Committee with our thanks. (Applause)

"We will proceed with nominations for the Chairman of the Board of Governors."

Dr. Charles A. Doan was nominated by Dr. Charles E. Watts, seconded by Dr. James O. Ritchey, who also moved that nominations be closed and a unanimous ballot cast for Dr. Doan.

The motion was put to vote and Dr. Charles A. Doan was declared elected as Chairman of the Board of Governors for a term of three years.

CHAIRMAN PALMER: "This action still more complicates matters. Since Dr. Doan was the Vice Chairman, we must now elect a new Vice Chairman."

Dr. Robert Wilson, Jr., nominated Dr. Carter Smith, of Atlanta; the nomination was seconded by Dr. C. D. Briscoe. It was moved by Dr. J. Murray Kinsman that nominations be closed. The motions were put to vote, and Dr. Carter Smith was unanimously elected Vice Chairman for a term of three years.

DR. DOAN: "Although I have been previously your Vice Chairman, I know we all felt that the position of leadership as Chairman on this Board could not be replaced. The Nominating Committee of the College, however, chose to remove our Chairman, Dr. Palmer, by nominating him to the Board of Regents. They were persuaded that the Board of Regents should have the benefit of his counsel and, perhaps, be a protagonist for the Board of Governors when we bring to the Regents some of the deliberations that we have in mind. We have worried a little about how he would fare in that body, but he seems, as our representative in the past, to have done all right. Perhaps, either to protect himself or to call order in the Board of Regents, he might need this Gavel, which has been properly inscribed on behalf of the Board of Governors, and will remind him of his term of service as our Chairman." (Presents Gavel)

CHAIRMAN PALMER: "Thank you very much. This is deeply appreciated. I must admit that I wonder why I, at what seems to be an early age, was turned out to grass."

At the request of the Chairman, the Secretary read several pertinent announcements.

CHAIRMAN PALMER: "I think the three Governors whose maximal terms expire and who are not eligible for re-election are Doctors Poindexter, of Idaho, Fort of Maryland and Archer of Mississippi. I have retained this Chair instead of turning it over to Dr. Doan as I should, because I wanted to have the privilege and pleasure of expressing to these three men the appreciation of the College for their splendid service as Governors. I will ask them to stand." (Applause)

Adjournment, 3:00 p.m.

Attest: E. R. LOVELAND,
Secretary

ABSTRACT, MINUTES OF THE BOARD OF REGENTS, ST. LOUIS, MO., APRIL 13, 1951

The third meeting of the Board of Regents during the 32nd Annual Session of the American College of Physicians was held at St. Louis, Mo., Friday, April 13, 1951, at 12:30 p.m., with President Maurice C. Pincoffs presiding and Mr. E. R. Loveland acting as Secretary, and the following in attendance:

Maurice C. Pincoffs	*President*
T. Grier Miller	*President-Elect*
LeRoy H. Sloan	*First Vice President*
Walter B. Martin	*Second Vice President*
Howard P. Lewis	*Third Vice President*
William D. Stroud	*Treasurer*
Asa L. Lincoln	
Walter L. Palmer	
Edward L. Bortz	
Harold H. Jones	
Dwight L. Wilbur	
Charles F. Moffatt	
A. B. Brower	
Alex M. Burgess	
George H. Lathrope	
Cyrus C. Sturgis	
Charles A. Doan	

The Secretary, after recording the roll, read an abstract of the Minutes of the preceding meeting of the Board of Regents, which, after one correction, was approved.

The Board of Regents entertained Dr. Clarence B. Whims, F.A.C.P., and Mr. Albert Skean, Director of the Atlantic City Convention Bureau, who presented an invitation, supported by all members from New Jersey, for the College to hold its 1953 Annual Session in Atlantic City. They outlined their facilities and made suggestions concerning ways and means by which the College could conduct successfully its Annual Session.

Dr. Leland Hawkins, F.A.C.P., College Governor for Southern California, spoke concerning the facilities of Los Angeles for an Annual Session of the College, and predicted the members in Los Angeles might be prepared and would like to entertain the Annual Session of the College there in 1954 or 1955.

Mr. Fred Puffer, of the Chicago Convention Bureau, presented an invitation for the 1953 Session of the College to be held in Chicago. He, too, outlined the advantages and facilities of his city.

President Pincoffs thanked the visitors for their invitations and assured them that the Board of Regents would carefully weigh all considerations later in the meeting, in order to determine upon the 1953 meeting place.

President Pincoffs: "Through the expiration of the term of Dr. George Morris Piersol, the office of Secretary-General becomes vacant, and Dr. Piersol has formally stated that he does not wish to accept renomination. His services to this College in this office covered a most critical period, rebirth and troubled adolescence and early vigorous manhood of the College. Morris Piersol's high ideals, his wisdom, his devotion to the College, his high standing in the world of American medicine, have made him an ideal Secretary-General. His lovable personality, which won men to his views, has endeared him to the successive Officers and Regents of the College and

also to the membership of this College. In turn, the College has given to him, with the acclaim of its members, its highest honors, and I would not want this first meeting of the Regents in which his successor is to be elected to pass without this record in our Minutes of the gratitude, the admiration and the thanks of the Regents for George Morris Piersol."

On motion by Dr. Cyrus C. Sturgis, seconded by several and carried, it was

RESOLVED, that the comment of President Maurice C. Pincoffs be considered a resolution of the Board of Regents and spread verbatim in the Minutes.

Dr. George H. Lathrope placed in nomination for Secretary-General the name of Dr. Richard A. Kern, of Philadelphia. The nomination was seconded and by motion, duly made and carried, nominations were closed and a unanimous ballot was cast making Dr. Kern the Secretary-General.

Dr. Edward L. Bortz nominated Dr. William D. Stroud for re-election as Treasurer. The nomination was seconded and, there being no other nominations, Doctor Stroud was declared re-elected by unanimous vote.

In accordance with provisions of the By-Laws and/or regulations of the Board of Regents, President Pincoffs announced the personnel of new committees for the year 1951–52. The personnel of these committees have already been published elsewhere in this journal (June, 1951 issue) and are not repeated at this point.

The Board of Regents made nominations of four Fellows from which vacancies on the American Board of Internal Medicine shall be filled in the cases of the expiring terms of Dr. Truman G. Schnabel, Philadelphia, and Dr. Alex. M. Burgess, Providence. These four nominations were submitted to the American Board of Internal Medicine for its selection of two, the incumbents to serve for terms of three years starting July 1, 1951.

The Chairman of the Board of Governors, Dr. Charles A. Doan, was instructed to make appointments to the Governors' Advisory Committee on Postgraduate Courses and, following the meeting, announced the Committee personnel as follows:

THOMAS M. MCMILLAN, Philadelphia, *Chairman*
WARD DARLEY, Denver
CHESTER S. KEEFER, Boston
KARVER L. PUESTOW, Madison
IRVING S. WRIGHT, New York

President Pincoffs, in accordance with the regulations of the By-Laws, reserved for the time being the naming of the personnel of the Committee on Nominations, but subsequently announced the following:

A. B. BROWER (Regent), Dayton, *Chairman*
CHARLES F. MOFFATT (Regent), Montreal
THOMAS FINDLEY (Governor), New Orleans
BENJAMIN F. WOLVERTON (Governor), Cedar Rapids
WETHERBEE FORT (Fellow-at-Large), Baltimore

PRESIDENT PINCOFFS: "We shall now have the report of the Chairman of the Board of Governors, Dr. Charles A. Doan."

DR. CHARLES A. DOAN: "Mr. President and Regents: Following the presentation of the Governors' Survey Committee on Sunday, April 8, the Committee members discussed with members of the Board of Governors and the Board of Regents some of the implications of the recommendations of the report, and we came back after an interim meeting to the Board of Governors on Wednesday, April 11, and presented a further recommendation, attempting and intending to implement the general report that was made first and the supplemental recommendations thereto, which, after dis-

cussion, was accepted by the Board of Governors with one dissenting vote, and we were instructed to present the supplemental recommendations to the Board of Regents at this time for its consideration.

The Committee recommends:

(1) Certification by the American Board of Internal Medicine, or other appropriate board, shall be a prerequisite for election to Associateship in the College;
(2) There shall be no limit to the term of Associateship, except under circumstances of grave professional or personal misconduct;
(3) Associates of the College, prior to consideration for election to Fellowship shall (a) have been an Associate for at least three years, and (b) show evidence of progressive professional attainment and advancement.

"I, therefore, have the privilege of presenting, Mr. President, this recommendation with one dissenting vote from the Board of Governors for the consideration of the Board of Regents."

PRESIDENT PINCOFFS: "I suggest that we confine our action at this moment to acknowledge receipt of the report from the Chairman of the Board of Governors and defer consideration or action on this report. Further discussion of this will come up among other business at a later time."

DR. PALMER: "As retired Chairman of the Board of Governors, I would like to say that during my six years on that Board, I think I have never seen the Board of Governors react as favorably on anything as they did on Dr. Doan's report. I was much surprised, because, as we all know, this is a general subject which has been under discussion for a good many years by the Board of Governors, and at all previous suggestions from the Credentials Committee or any other source, providing that certification shall be a prerequisite for Associateship, the Board of Governors has voted against it. The fact that they reversed themselves on this occasion, I think, is a great tribute to the persuasiveness of Dr. Doan's recommendation, and also to the fact that he had considered various other aspects of the situation and had emphasized them, such as the dropping of so many Associates from the College Roster at this meeting, because they had not been able to qualify for Fellowship. The Board of Governors feels quite strongly that something should be done to correct that, and believes that Dr. Doan's suggestion of indefinite tenure of Associateship would remedy it without necessarily increasing greatly the size of the College, unless the Credentials Committee lets the bars down. Of course, we understand that at the present time somewhat more than half of the Associates are already certified before election. The new proposal would decrease the number of elections to Associateship at the present time. On the other hand, the number of Associates would be increased, because they would not be dropped at the end of five years. That seemed to the Board of Governors to have merit. Personally, I had a little reservation with regard to tying the hands of the Credentials Committee so completely, and the thought occurred to me it might be well to insert after that first point, requiring certification by some board, a phrase indicating that under certain exceptional circumstances, or except under exceptional circumstances, the Credentials Committee might accept a candidate without that certification.

"Now, on second thought, that may not be necessary, because it is still possible for the Credentials Committee to recommend for Direct Fellowship a candidate who is so meritorious that the College needs him, even though he be not certified. I have spoken primarily to emphasize the strong approval of the Board of Governors of the report of Dr. Doan's Committee."

PRESIDENT PINCOFFS: "We shall consider this matter now. From my point of view, the questions that really come before the Regents now are not of blanket

approval with subsequent action, but one of determining in the first place whether the obvious merits of this proposal do not require that the Regents give them a period of careful consideration and analysis, so that we might come to this again at the November meeting with fuller knowledge of the implications. In the second place, if that is the consensus of the Board of Regents, could it not be best achieved by a committee appointed to work on this problem for the Regents, and to report at its next meeting? I have in mind a rather broad committee, because I think this is one of the very vital questions affecting the future of the College. Such a committee might contain three Regents or Officers, two members of the Board of Governors and one Fellow-at-Large. Of course, it is a matter for your decision and also whether you wish the President to appoint the Committee, or have them appointed by others, but I do strongly recommend to the Regents that at this time we decide only that this does require very careful consideration and a major policy change in the College, and that we defer until November any action that would affect the operations of the Governors or the Credentials Committee during the interim."

Dr. Cyrus C. Sturgis: "I am thoroughly in favor of this proposal, and I think the whole Board of Regents will be eventually, if they are not now. On the other hand, I do not believe we have anything to lose if we do appoint such a committee for a further analysis and then have a report. Therefore, I move that the President appoint a committee to analyze this matter further and to report at the November meeting of this Board."

The motion was seconded by Dr. T. Grier Miller and unanimously carried.

President Pincoffs: "Our next item of business is the appointment of a General Chairman for the Cleveland Annual Session next year. It has been customary for the President of the College to nominate to the Board of Regents some one for the post. I have given it a great deal of thought, and Mr. Loveland and I have consulted widely with Dr. Doan and others concerning the man best fitted, by his interest and by his personal status in the community, for the post, and I place before you the name of Dr. Roy W. Scott, of Cleveland, as General Chairman."

It was moved and seconded and carried that Dr. Roy W. Scott be elected General Chairman for the 1952 Annual Session.

The Secretary presented a communication from Mr. Charles A. Connor, the Medical Director of the American Heart Association, who pointed out that the American College of Physicians is entitled to have a second representative on the American Council on Rheumatic Fever and recommended that the College appoint another representative in addition to Dr. William D. Stroud, who presently is the sole College appointee.

On motion by Dr. Walter L. Palmer, seconded by Dr. William D. Stroud, Dr. Russell L. Cecil, F.A.C.P., New York City, was selected as the second College representative on the said Council.

The Secretary then presented a telegram from the Federal Civil Defense Administrator at Washington, requesting the College to send four or more of its leaders to the Federal Civil Defense Conference in Washington, May 7 and 8.

By resolution, the President was instructed to appoint the College representatives. He thereafter selected Drs. John Minor, Washington, Lemuel C. McGee, Wilmington, Eugene C. Eppinger, Boston, and agreed to attend himself as the fourth representative.

At this point in the proceedings, President Pincoffs brought up for more specific action the proposed Joint Commission on Accreditation of Hospitals. The matter was reviewed in great detail and its advantages and disadvantages were carefully weighed. A resolution was adopted authorizing the President and the Executive Committee to make selection of an appropriate individual to represent the American College of Physicians on the Advisory Committee of said Commission and also to make appointments of the A.C.P. Commissioners, selections to be made later.

After appropriate discussion of the various meeting place possibilities for 1953, the invitation from Atlantic City was unanimously accepted, and the date set for April 13–17.

In connection with the 1952 Annual Session at Cleveland, April 21–25, President Pincoffs requested aid and advice from all members of the Board of Regents and recommended in particular that the committees be authorized to invite as panel moderators or participants any individual, regardless of his membership in the College, with authorization to pay his travel expenses, a departure from the previous custom.

A motion was adopted providing that present regulations for the payment of non-members, as currently applied to non-members invited by the President to participate in the Morning Lectures and General Sessions, shall be extended to include also the Panel Discussion participants.

Adjournment.

Attest: E. R. LOVELAND
Secretary, Board of Regents